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Linaclotide in irritable bowel syndrome with constipation: A Phase 3 randomized trial in China and other regions

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Abstract

Background and Aim: Linaclotide is a guanylate cyclase-C agonist approved in multiple countries to treat irritable bowel syndrome with constipation (IBS-C). China has unmet need for well-tolerated therapy that is effective in treating both bowel and abdominal symptoms of IBS-C. This trial evaluated linaclotide's efficacy and safety in IBS-C patients in China and other regions.
Methods: This Phase 3, double-blind trial randomized IBS-C patients to once-daily oral 290-μg linaclotide or placebo at centers in China, North America, and Oceania. Patients reported bowel and abdominal symptoms daily; adverse events were monitored. Co-primary and secondary endpoints were tested using a predefined three-step serial gatekeeping multiple comparisons procedure.
Results: The intent-to-treat population included 839 patients (mean age = 41 years; 82% female; 81% Asian). The trial met all co-primary and secondary endpoints. Co-primary responder criteria were met by 60.0% of linaclotide patients *versus* 48.8% of placebo patients for abdominal pain/discomfort (≥ 30% decrease for ≥ 6/12 weeks; $P < 0.05$), and 31.7% of linaclotide *versus* 15.4% of placebo patients for IBS degree of relief (score ≤ 2 for ≥ 6/12 weeks; $P < 0.0001$). Secondary 12-week change-from-baseline endpoints (spontaneous bowel movement/complete spontaneous bowel movement frequency, stool consistency, straining, abdominal pain, abdominal discomfort, and abdominal bloating) were significantly improved with linaclotide *versus* placebo (all $P < 0.0001$). Diarrhea was the most common adverse event (9.4% linaclotide, 1.2% placebo). Discontinuation rates due to diarrhea were low (0.7% linaclotide, 0.2% placebo).
Conclusions: Once-daily 290-μg linaclotide improved bowel habits, abdominal symptoms, and global measures in a predominantly Chinese IBS-C population.

Introduction

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder in which abdominal pain and discomfort are associated with altered defecation.[1] IBS prevalence varies widely across countries, with higher prevalence in women than men.[2,3] A recent literature review by the Rome Foundation working team found an IBS prevalence of 9.6% in Asia and 8.1% in North America/Europe/Australia/New Zealand.[4] Prevalence estimates within China range from 1% to 18% using Rome I/II criteria and 5% to 16% using Rome III criteria.[2,5] IBS is subtyped based on predominant stool pattern; approximately one-third of IBS patients are classified as having IBS with constipation (IBS-C).[1,6,7] IBS-C is characterized by abdominal symptoms (pain, discomfort, and bloating), reduced stool frequency, hard/lumpy stools, straining during bowel movements (BMs), and a sensation of incomplete evacuation.[8]

The China Food and Drug Administration (FDA) regulatory guidelines require a Phase 3 international multicenter clinical trial with enrollment primarily in China for marketing application. Therefore, this registration trial to enable marketing application in

China primarily enrolled patients in China with additional patients enrolled in North America and Oceania. Although multiple medicines have been used in China for treating IBS symptoms, there are currently no treatments approved by the China FDA specifically for IBS-C. Of the available treatments, antispasmodic therapies primarily address abdominal pain with limited effects on bowel symptoms, while laxatives, bulking agents, and lactulose are widely used to relieve constipation symptoms but do not address abdominal symptoms.[9,10] Therefore, there is an unmet medical need in China for therapy that is well tolerated and effective in treating both the bowel and abdominal symptoms of IBS-C.

Linaclotide has been approved in the United States, European Union, Switzerland, Canada, Mexico, and Hong Kong (290 μg), and Japan (500 μg) for the treatment of IBS-C in adults (once-daily oral dosing). Linaclotide, a synthetic, minimally absorbed, 14-amino-acid peptide, is a potent and selective guanylate cyclase-C agonist. Linaclotide acts locally in the intestinal lumen, stimulating guanylate cyclase-C and resulting in increased production of cyclic guanosine monophosphate, which induces fluid secretion and accelerates intestinal transit.[11–13] In animal models, linaclotide reduced visceral hypersensitivity through cyclic guanosine monophosphate modulation of afferent nerve activity, suggesting an analgesic mechanism of action independent of bowel function improvement.[14–16] In two Phase 3 trials conducted in North America, linaclotide demonstrated improvement in both the bowel and abdominal symptoms of IBS-C in adult men and women.[17–19]

The objective of this trial was to assess the efficacy and safety of linaclotide 290 μg, administered orally once daily, in IBS-C patients in China and other regions.

Methods

Design overview. This Phase 3, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week trial was conducted at 98 clinical centers in China, North America (USA and Canada), and Oceania (Australia and New Zealand). Patients with medically recorded IBS-C (newly diagnosed or previously diagnosed) were recruited between July 2013 and January 2015; the first patient was randomized on August 14, 2013, and the last patient completed on 05 May 2015. The trial was designed, conducted, and reported in compliance with Good Clinical Practice guidelines and according to the ethical principles originating in the Declaration of Helsinki. An Ethics Committee/Institutional Review Board approved the protocol and all trial procedures. All patients provided written informed consent before participating in any trial-related procedures. The trial is registered at ClinicalTrials.gov (registration number NCT01880424).

The randomization sequence was generated in SAS by a statistical programmer not otherwise involved in this trial. Patients were assigned to treatment employing a central randomization accessed by the trial coordinator via an interactive response system. Blocks of eight treatment assignments (1:1 ratio) were allocated to individual sites, and within-site assignments were determined by the order of interactive response sessions.

During a screening period lasting ≤ 21 days, patients provided blood and urine samples for laboratory testing and were instructed to discontinue prohibited medications (including laxatives, suppositories, enemas, and traditional Chinese medicines). Patients meeting the inclusion/exclusion criteria then entered a 14- to 21-day pretreatment baseline period during which they entered daily and weekly symptom assessments into an electronic diary (eDiary). Subsequently, eligible patients were randomized to receive linaclotide 290 μg or matching placebo (identical in appearance and containing the same inactive substances), administered as an oral capsule once daily throughout the 12-week treatment period. Patients were instructed to take study drug ≥ 30 min before breakfast and to report symptoms via eDiary daily throughout the treatment period. For 14 days immediately following the treatment period (i.e. the post-treatment period), patients continued daily symptom reporting.

Trial visits were scheduled at screening, the start of the baseline period, randomization (day 1), throughout the treatment period (weeks 2, 4, 8, and 12), and the end of the post-treatment period (week 14). All patients and personnel involved in the trial's design and implementation remained blinded to treatment assignments until the database was locked.

Trial patients. Men and women ≥ 18 years of age were eligible if they met the Rome III IBS criteria.[20] In the 3 months before screening (with symptom onset ≥ 6 months prior), patients had to report < 3 BMs per week and ≥ 1 additional bowel symptom during > 25% of BMs (straining, lumpy/hard stools, or sensation of incomplete evacuation). During the 14 days before the randomization visit, patients also had to report an average of ≤ 5 spontaneous BMs (SBMs) per week (SBM = a BM without laxative, suppository, or enema use in the preceding 24 h) and < 3 complete SBMs (CSBMs) per week (CSBM = an SBM that is associated with a sense of complete evacuation) and had to report abdominal pain ≥ 2 days each week with an average score ≥ 3.0 on a 0- to 10-point numerical rating scale. Women of childbearing potential were required to use contraceptives and have negative pregnancy tests at the screening and randomization visits (before dosing).

Patients were excluded if they reported loose/mushy or watery stool (Bristol Stool Form Scale [BSFS] score of 6 or 7) in the absence of laxative, suppository, enema, or other prohibited medication use, for > 25% of BMs during the 3 months before screening; reported a BSFS score of 6 for > 1 SBM or 7 for any SBM during the 14 days before the randomization visit; or used rescue medicine (bisacodyl tablet or suppository) or other laxative, suppository, or enema on the calendar day before or day of the randomization visit.

Efficacy assessments and endpoints. Daily patient reports via eDiary included severity of abdominal pain at its worst, abdominal discomfort, abdominal bloating, abdominal cramping, and abdominal fullness (all on a 0- to 10-point numerical rating scale, with higher score indicating greater severity) during the previous 24 h. Patients also reported daily assessments of BMs, including the number and time of BMs since the previous day's call, and whether rescue medication or other laxatives, suppositories, or enemas were used. For each BM, patients reported whether it was associated with a sensation of complete emptying (yes/no); stool consistency (7-point BSFS; 1 = "separate hard lumps like

nuts [difficult to pass]" to 7 = "watery, no solid pieces [entirely liquid]"); and severity of straining (5-point ordinal scale; 1 = "not at all" to 5 = "an extreme amount").

Weekly eDiary assessments included degree of relief of IBS symptoms (7-point balanced ordinal scale; 1 = "completely relieved", 4 = "unchanged", 7 = "as bad as I can imagine"), constipation severity and IBS symptom severity (both on a 5-point ordinal scale; 1 = "none" to 5 = "very severe"), adequate relief of IBS symptoms (yes/no), and treatment satisfaction (5-point ordinal scale; 1 = "not at all satisfied" to 5 = "very satisfied").

Co-primary endpoints. The trial had two co-primary responder endpoints (the same endpoints used for European Medicines Agency [EMA] submission of the linaclotide Phase 3 IBS-C trials conducted in North America). The 12-week abdominal pain/abdominal discomfort responder endpoint defined a responder as a patient who had ≥ 30% reduction in average weekly abdominal pain or abdominal discomfort score, with neither weekly score worsening from baseline (i.e. abdominal pain/abdominal discomfort weekly responder), for ≥ 6 of 12 weeks. The 12-week IBS degree of relief responder endpoint defined a responder as a patient who had a weekly IBS degree of relief score ≤ 2 ("considerably relieved" or "completely relieved") (i.e. IBS degree of relief weekly responder) for ≥ 6 of 12 weeks.

Secondary and additional endpoints. Secondary endpoints assessed the 12-week average change from baseline in weekly CSBM and SBM frequency rate, stool consistency, straining, abdominal bloating, abdominal pain, and abdominal discomfort.

A number of additional endpoints were also assessed, including sustained responder endpoints corresponding to the co-primary endpoints (patients had to meet weekly responder criteria for ≥ 6 of 12 weeks including ≥ 2 of the last four treatment weeks); abdominal pain, CSBM, and multi-symptom abdominal pain/CSBM responder endpoints (corresponding to primary endpoints from the linaclotide Phase 3 IBS-C trials conducted in North America[17,18]); weekly average change-from-baseline endpoints (CSBM/SBM frequency, stool consistency, straining, abdominal pain, abdominal discomfort, and abdominal bloating); 12-week average percent change from baseline in abdominal pain, abdominal discomfort, and abdominal bloating; time to first SBM (hours from first study drug dose to first SBM); proportion of patients who had a CSBM/SBM within 24 h of first receiving study drug; 12-week average change from baseline in abdominal cramping, abdominal fullness, IBS symptom severity, and constipation severity; global responder endpoints (IBS symptom severity, constipation severity, and adequate relief); and average treatment satisfaction at week 12. A post hoc exploratory analysis using the weekly responder criteria for the co-primary endpoints was also conducted.

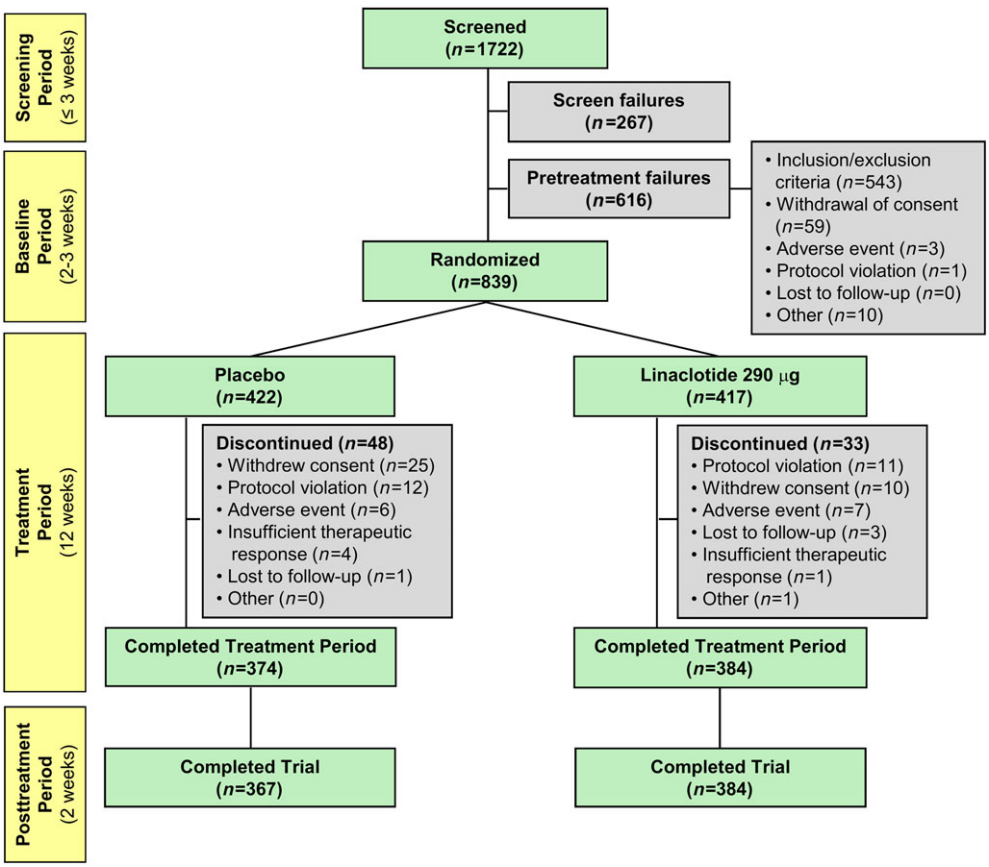

Figure 1 Patient flow through the trial. [Color figure can be viewed at wileyonlinelibrary.com]

All endpoints presented were prespecified, unless otherwise noted. Several additional endpoints not in the protocol were subsequently added in the statistical analysis plan, which was finalized while the trial was ongoing (and data remained blinded).

Safety assessments. At each scheduled trial visit, all patients were asked a nonleading question regarding adverse events (AEs). The investigator evaluated all patient-reported AEs and serious AEs (SAEs) for severity and relationship to study drug. Clinical laboratory tests, vital sign measurements, electrocardiograms, and physical examinations were conducted.

Statistical analysis. Based on results from a previous Phase 3 IBS-C trial,[19] a sample size of 800 patients (400 per treatment group) was determined to provide 95% power to detect a difference between linaclotide and placebo in both co-primary endpoints. The overall family-wise Type I error rate for testing the co-primary and secondary endpoints was controlled at the 0.05 significance level using a three-step serial gatekeeping multiple comparisons procedure. There was no Type I error control for the additional endpoints. Statistical analyses were performed using SAS for Windows (version 9.3).

Responder endpoints were analyzed using Cochran–Mantel–Haenszel tests controlling for geographic region; patients who could not be assessed because of missing information were considered non-responders for that endpoint. Continuous change-from-baseline and percent-change-from-baseline endpoints were analyzed using an analysis of covariance model with fixed-effect terms for treatment group and geographic region and the corresponding baseline value as a covariate. Means presented are least-squares means (i.e. means adjusted for the other effects) from the analysis of covariance model. Treatment satisfaction was analyzed for each treatment-period week using an ANOVA with fixed-effect terms for treatment group and geographic region. For time to first SBM, the time-to-event distribution for linaclotide *versus* placebo was compared using a log–rank test stratified by geographic region.

Efficacy analyses were based on the intent-to-treat population (all randomized patients). Safety analyses were based on the safety population (randomized patients who received ≥ 1 dose of study drug).

Results

Patient disposition, demographics, and baseline characteristics. Of 1722 patients who were screened for this trial, 839 patients were randomized (Fig. 1). All randomized patients were included in intent-to-treat population (417 linaclotide and 422 placebo patients); 835 patients received ≥ 1 dose of study drug and were included in the safety population (416 linaclotide and 419 placebo patients). In total, 758 patients (90.3% of patients randomized) completed the 12-week treatment period, and 751 patients (89.5%) completed the trial. Demographics and baseline clinical characteristics were well balanced across treatment groups; overall, 82.0% of patients were female, 80.6% were Asian, and 78.5% were enrolled in China (Table 1).

Table 1 Summary of patient demographic and baseline characteristics (ITT population)

	Placebo (n = 422)	Linaclotide 290 μg (n = 417)
Demographic data		
Age (years), mean (range)	41.3 (18–80)	41.0 (18–77)
≥ 65 years, *n* (%)	17 (4.0)	17 (4.1)
Sex, *n* (%)		
Female	355 (84.1)	333 (79.9)
Male	67 (15.9)	84 (20.1)
Race, *n* (%)		
Asian	338 (80.1)	338 (81.1)
Caucasian	70 (16.6)	64 (15.3)
Black/African American	12 (2.8)	15 (3.6)
Other	2 (0.5)	0
Geographic region		
China	332 (78.7)	327 (78.4)
North America	72 (17.1)	67 (16.1)
Oceania	18 (4.3)	23 (5.5)
Body mass index (kg/m^2), mean (SD)	23.4 (4.4)	23.2 (4.4)
Baseline data, mean (SD)		
Abdominal pain (11-point NRS)	5.2 (1.5)	5.2 (1.5)
Abdominal discomfort (11-point NRS)	5.4 (1.7)	5.4 (1.7)
Abdominal bloating (11-point NRS)	5.6 (1.9)	5.6 (1.9)
CSBMs/week	0.2 (0.5)	0.3 (0.6)
SBMs/week	1.6 (1.2)	1.7 (1.2)
Stool consistency score (7-point BSFS)	2.5 (1.2)	2.6 (1.1)
Straining score (5-point ordinal scale)	3.3 (0.9)	3.2 (0.9)

BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; ITT, intent-to-treat; NRS, numerical rating scale; SBM, spontaneous bowel movement.

Efficacy. The trial met the statistical significance criteria under the multiple comparisons procedure for the co-primary and all secondary efficacy endpoints.

A total of 60.0% of linaclotide-treated patients (250 of 417 patients) met the co-primary abdominal pain/abdominal discomfort endpoint responder requirements, compared with 48.8% of patients (206 of 422 patients) in the placebo group (P = 0.0010; odds ratio 1.59; 95% confidence interval [1.21, 2.09)]; Table 2), with a number needed to treat of 8.9. A total of 31.7% of linaclotide-treated patients (132 of 417 patients) met the co-primary IBS degree of relief endpoint responder requirements, compared with 15.4% of patients (65 of 422 patients) in the placebo group ($P < 0.0001$; odds ratio 2.56; 95% confidence interval [1.83, 3.58)]; Table 2), with a number needed to treat of 6.1. Higher weekly responder rates corresponding to the co-primary endpoints were seen among linaclotide-treated patients *versus* placebo-treated patients within the first 2 weeks and sustained through week 12 ($P < 0.05$ at weeks 2–12 for abdominal pain/discomfort and all weeks for IBS degree of relief; post hoc exploratory analysis; Fig. 2). When patients had to meet sustained responder criteria, both abdominal pain/abdominal discomfort and IBS degree of relief responder rates were similar to those for the co-primary endpoints (Table 3).

For all secondary endpoints, which measured change from baseline in bowel and abdominal symptoms, patients treated with linaclotide showed significant improvement relative to

Table 2 Co-primary efficacy endpoint results (ITT population)

Co-primary endpoints	Placebo (n = 422) n (%)	Linaclotide 290 μg (n = 417) n (%)	P-value[†]
≥ 30% weekly mean decrease in abdominal pain or discomfort, with neither weekly score worsening from baseline, for ≥ 6/12 weeks	206 (48.8)	250 (60.0)	0.0010
Degree of relief of IBS symptoms weekly scores of "considerably relieved" or "completely relieved" for ≥ 6/12 weeks	65 (15.4)	132 (31.7)	<0.0001

[†]P-values based on comparison of linaclotide *versus* placebo using a CMH test; for both co-primary endpoints, linaclotide demonstrated statistically significant improvement *versus* placebo, controlling for multiplicity.
CMH, Cochran–Mantel–Haenszel; IBS, irritable bowel syndrome; ITT, intent-to-treat.

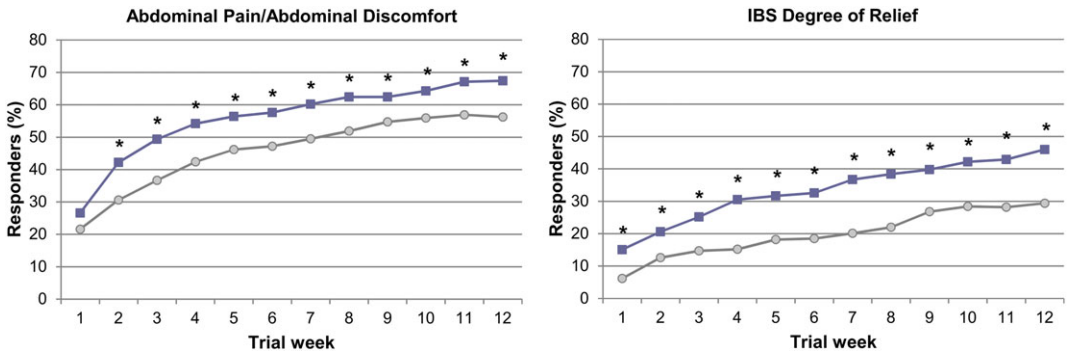

Figure 2 Abdominal pain/abdominal discomfort and IBS degree of relief weekly responders over the 12-week treatment period (ITT population). Post hoc exploratory analysis outside the MCP using weekly responder criteria for each of the co-primary endpoints. *$P < 0.05$; nominal P-values for linaclotide *versus* placebo using a CMH test. CMH, Cochran–Mantel–Haenszel; IBS, irritable bowel syndrome; ITT, intent-to-treat; MCP, multiple comparisons procedure. —○—, placebo; —■—, linaclotide 290 μg. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3 Secondary and additional efficacy results during the 12-week treatment period (ITT population)

	Placebo (n = 422)	Linaclotide 290 μg (n = 417)	P-value
Multi-symptom responder endpoints			
% of patients with ≥30% weekly mean decrease in abdominal pain or discomfort, with neither weekly score worsening from baseline, for ≥6/12 weeks, including ≥ 2 of the last 4 weeks[†]	48.6	58.3	0.0037[¶]
% of patients with ≥ 30% weekly mean decrease in abdominal pain and an increase in ≥ 1 CSBM/week from baseline, for ≥ 6/12 weeks[†]	21.3	34.8	< 0.0001[¶]
% of patients with ≥ 30% weekly mean decrease in abdominal pain, ≥ 3 CSBMs/week, and an increase in ≥ 1 CSBM/week from baseline, for ≥ 9/12 weeks[†]	5.0	13.2	< 0.0001[¶]
Degree of relief of IBS symptoms			
Mean IBS degree of relief score (1–7)[††]	3.3	2.9	
Change from baseline, mean[††,‡‡]	−0.6	−1.0	< 0.0001[¶]
% of patients reporting weekly scores of "considerably relieved" or "completely relieved" for ≥ 6/12 weeks, including ≥ 2 of the last 4 weeks[†]	14.7	30.7	< 0.0001[¶]
Abdominal pain			
Mean abdominal pain score (11-point NRS)[††]	3.8	3.3	
Change from baseline, mean[††,‡‡]	−1.1	−1.6	< 0.0001[§§]
% change from baseline, mean[††,‡‡]	−20.6	−29.7	< 0.0001[¶]
% of patients with ≥ 30% weekly mean decrease in abdominal pain from baseline for ≥ 9/12 weeks[†]	32.7	43.9	0.0007[¶]

(Continues)

Table 3. (Continued)

	Placebo (n = 422)	Linaclotide 290 μg (n = 417)	P-value
Abdominal discomfort			
Mean abdominal discomfort score (11-point NRS)[††]	4.1	3.6	
Change from baseline, mean[††,‡‡]	−1.0	−1.5	< 0.0001[§§]
% change from baseline, mean[††,‡‡]	−18.1	−25.8	0.0005[¶]
Abdominal bloating			
Mean abdominal bloating score (11-point NRS)[††]	4.4	3.8	
Change from baseline, mean[††,‡‡]	−0.9	−1.5	<0.0001[§§]
% change from baseline, mean[††,‡‡]	−17.3	−26.2	0.0002[¶]
CSBMs			
Mean CSBMs/week [††]	1.1	2.2	
Change from baseline in CSBMs/week, mean[††,‡‡]	1.0	1.9	< 0.0001[§§]
% of patients with ≥ 3 CSBMs/week and an increase in ≥ 1 CSBM/week from baseline for ≥ 9/12 weeks[†]	7.3	19.9	< 0.0001[¶]
% of patients with CSBM ≤ 24 h after first dose of study drug[¶]	6.4	17.0	< 0.0001[¶]
SBMs			
Mean SBMs/week[††]	2.9	4.4	
Change from baseline in SBMs/week, mean[††,‡‡]	1.5	3.0	< 0.0001[§§]
% of patients with SBM ≤ 24 h after first dose of study drug[¶]	28.9	48.7	< 0.0001[¶]
Time to first SBM after first dose of study drug, median number of hours[‡]	43.7	24.4	< 0.0001[¶]
Stool consistency			
Mean BSFS score (1–7)[††]	3.4	4.2	
Change from baseline, mean[††,‡‡]	0.8	1.5	< 0.0001[§§]
Straining			
Mean straining score (1–5)[††]	2.4	2.0	
Change from baseline, mean[††,‡‡]	−0.7	−1.0	< 0.0001[§§]
IBS symptom severity			
Mean IBS symptom severity score (1–5)[††]	2.8	2.5	
Change from baseline, mean[††,‡‡]	−0.5	−0.8	< 0.0001[¶]
% of patients with a decrease of ≥ 1 in weekly IBS symptom severity score from baseline for ≥ 6/12 weeks[¶]	44.1	57.6	< 0.0001[¶]
Constipation severity			
Mean constipation severity score (1–5)[††]	2.9	2.5	
Change from baseline, mean[††,‡‡]	−0.6	−1.0	< 0.0001[¶]
% of patients with a decrease of ≥ 1 in weekly constipation severity score from baseline for ≥ 6/12 weeks[¶]	46.0	65.0	< 0.0001[¶]
Adequate relief of IBS symptoms			
% of patients reporting adequate relief for ≥ 6/12 weeks[¶]	31.0	44.6	< 0.0001[¶]
Treatment satisfaction			
Mean treatment satisfaction score at week 12 (end of treatment) (1–5) [§]	2.7	3.0	0.0001[¶]

[†] P-values based on comparison of linaclotide *versus* placebo using a CMH test.
[‡] P-values based on comparison of the linaclotide *versus* placebo time-to-event distributions using a log–rank test.
[§] P-values based on comparison of linaclotide *versus* placebo using an ANOVA model.
[¶] Additional endpoint.
[††] Means over the 12-week treatment period.
[‡‡] Changes from baseline are LS means from an ANCOVA model; P-values based on comparison of linaclotide *versus* placebo using an ANCOVA model.
[§§] Secondary endpoint.
ANCOVA, analysis of covariance; BSFS, Bristol Stool Form Scale; CMH, Cochran–Mantel–Haenszel; CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome; ITT, intent-to-treat; LS, least-squares; NRS, numerical rating scale; SBM, spontaneous bowel movement.
For all secondary endpoints, linaclotide demonstrated statistically significant improvement *versus* placebo, controlling for multiplicity.

placebo over the 12-week treatment period (all $P < 0.0001$; Table 3). Improvements with linaclotide *versus* placebo were observed within the first week and sustained through week 12, as shown in weekly change-from-baseline analyses (additional endpoints; Fig. 3).

A subgroup analysis of the primary and secondary endpoints by geographic region showed higher responder rates and greater improvements from baseline with linaclotide *versus* placebo, regardless of geographic region (Table S1). Responder rates for the co-primary efficacy endpoints in both treatment

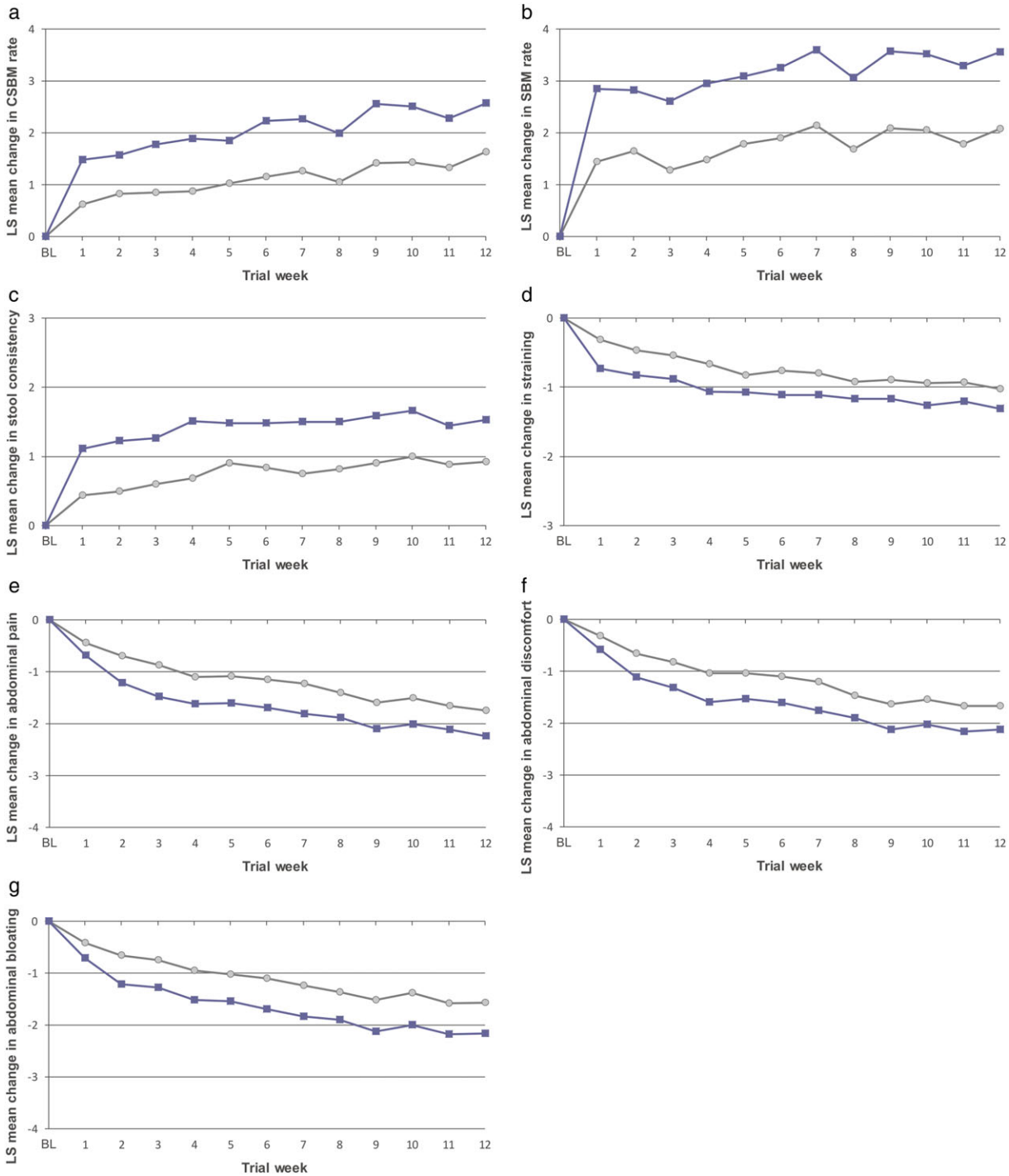

Figure 3 Change from baseline in bowel habits and abdominal symptoms during each week of the treatment period (ITT population). Additional endpoints; least-squares mean changes from baseline during each week using an observed-cases approach. (a) CSBM frequency rate; $P < 0.0001$ at all weeks. (b) SBM frequency rate; $P < 0.0001$ at all weeks. (c) Stool consistency; $P < 0.0001$ at all weeks. (d) Straining; $P < 0.001$ at all weeks. (e) Abdominal pain; $P < 0.01$ at all weeks. (f) Abdominal discomfort; $P < 0.01$ at all weeks. (g) Abdominal bloating; $P < 0.01$ at all weeks. All nominal *P*-values for linaclotide *versus* placebo using an ANCOVA model. ANCOVA, analysis of covariance; CSBM, complete spontaneous bowel movement; ITT, intent-to-treat; LS, least-squares; SBM, spontaneous bowel movement. —●—, placebo; —■—, linaclotide 290 μg. [Color figure can be viewed at wileyonlinelibrary.com]

groups were higher in China compared with Oceania and North America, but results in North America and Oceania were variable, likely because of the smaller sample sizes in the subgroups.

Additionally, a greater proportion of linaclotide *versus* placebo patients met the responder requirements for additional endpoints corresponding to the four primary responder endpoints from the linaclotide Phase 3 IBS-C trials conducted in North America (Table 3).[17,18] These endpoints required improvement from baseline in abdominal pain and CSBM frequency rate (i.e. ≥ 30% reduction in abdominal pain and an increase in ≥ 1 CSBM per week, in the same week) for ≥ 6 of 12 weeks (the endpoint recommended by the US FDA[21]; $P < 0.0001$); or improvement in abdominal pain (i.e. ≥ 30% reduction in abdominal pain), CSBM frequency rate (i.e. ≥ 3 CSBMs and an increase in ≥ 1 CSBM), or both, for ≥ 9 of 12 weeks (all $P < 0.001$).

Linaclotide-treated patients experienced shorter times from first dose of study drug to first SBM than placebo-treated patients, with median times of 24.4 and 43.7 h, respectively ($P < 0.0001$; Table 3).

Additional global measures (including change-from-baseline and responder endpoints related to IBS symptom severity, constipation severity, and adequate relief of IBS symptoms) were also improved with linaclotide *versus* placebo ($P < 0.0001$; Table 3). At the end of treatment, mean treatment satisfaction scores were higher in linaclotide-treated *versus* placebo-treated patients (3.0 *versus* 2.7; $P = 0.0001$).

Linaclotide also demonstrated greater improvements from baseline and responder rates compared with placebo for other additional efficacy endpoints ($P < 0.01$; Tables 3 and S2).

Safety. A total of 126 patients (30.3%) in the linaclotide group and 114 patients (27.2%) in the placebo group reported ≥ 1 treatment-emergent AE (TEAE; Table 4). Most TEAEs were mild or moderate in severity; 1.7% of linaclotide-treated patients and 1.9% of placebo-treated patients experienced one or more severe TEAEs. Diarrhea was the most frequently reported TEAE among linaclotide-treated patients, reported by 39 linaclotide patients (9.4%) and five placebo patients (1.2%). Diarrhea TEAEs were reported as mild or moderate in 37 of 39 linaclotide patients (94.9%) and all (5 of 5) placebo patients. Diarrhea was the most common AE leading to study drug discontinuation in the linaclotide group (three patients [0.7%] *versus* one placebo patient [0.2%]). No diarrhea SAEs or clinically significant complications of diarrhea (e.g. orthostatic hypotension or dehydration) were reported.

Table 4 Adverse events (safety population)

Adverse event	Placebo (n = 419) n (%)	Linaclotide 290 μg (n = 416) n (%)
Patients with any TEAE	114 (27.2)	126 (30.3)
Diarrhea	5 (1.2)	39 (9.4)
Upper respiratory tract infection	21 (5.0)	18 (4.3)
Nasopharyngitis	7 (1.7)	6 (1.4)
Increased alanine aminotransferase	6 (1.4)	6 (1.4)
Abdominal pain[†]	9 (2.1)	5 (1.2)
Upper abdominal pain[†]	2 (0.5)	5 (1.2)
Back pain	1 (0.2)	5 (1.2)

[†]All unique patients; no overlap between preferred terms.
TEAE, treatment-emergent adverse event.
TEAEs reported in ≥ 1.0% of linaclotide-treated patients.

Serious AEs were reported by four linaclotide patients (1.0%) and 10 placebo patients (2.4%). SAEs in linaclotide-treated patients were chronic obstructive pulmonary disease, ectopic pregnancy, induced abortion, and pericoronitis (one patient each). SAEs in placebo-treated patients were induced abortion (four patients), and bladder outlet obstruction, colitis, multiple system atrophy, non-cardiac chest pain, spontaneous abortion, and uterine leiomyoma (one patient each). (Per the protocol, all abortions were considered SAEs.) The investigator considered the spontaneous abortion (placebo group) to be possibly related to study drug; no other SAE was considered treatment-related. No deaths were reported.

There were no clinically significant differences between the linaclotide and placebo groups in the incidence of abnormal laboratory parameters, vital signs, or electrocardiogram parameters.

Discussion

This Phase 3, international, randomized, double-blind, placebo-controlled, 12-week clinical trial in IBS-C patients conducted in China, North America, and Oceania supports and expands on the results observed in two earlier linaclotide Phase 3 IBS-C trials conducted in North America.[17–19] This trial was not powered for statistical comparisons between geographic regions, a notable limitation; however, it provides important linaclotide data in a predominantly Chinese IBS-C population, which can be considered in the context of the previous North American trials. This is of particular interest because < 5% of patients in the previous North American trials were Asian and this trial is the first to evaluate linaclotide in a primarily Chinese population.

In this trial, linaclotide 290 μg showed significant improvement relative to placebo for both co-primary efficacy endpoints; 60.0% *versus* 48.8% of linaclotide-treated *versus* placebo-treated patients were 12-week abdominal pain/abdominal discomfort responders ($P = 0.0010$), and 31.7% *versus* 15.4% of patients were 12-week IBS degree of relief responders ($P < 0.0001$). The same co-primary endpoints were used for EMA submission of the linaclotide Phase 3 IBS-C trials conducted in North America, based on EMA guidance for evaluation of IBS treatments[22]; both the linaclotide and placebo groups in those trials had lower abdominal pain/abdominal discomfort responder rates (54.1–54.8% linaclotide *versus* 38.5–41.8% placebo) but slightly higher IBS degree of relief responder rates (37.0–39.4% linaclotide *versus* 16.6–18.5% placebo) compared with the current trial.[19]

More recent changes to the EMA guidelines for evaluation of IBS treatments suggest a primary responder endpoint for IBS-C consistent with that suggested by US FDA: ≥ 30% abdominal pain improvement and an increase in ≥ 1 CSBM per week from baseline for ≥ 50% of treatment weeks.[21,23] This was an additional endpoint in the current trial, with responder rates of 34.8% in the linaclotide group *versus* 21.3% in the placebo group ($P < 0.0001$, uncorrected). These data replicate the statistically

significant primary endpoint results in the linaclotide Phase 3 IBS-C trials conducted in North America, which showed responder rates of 33.6–33.7% in linaclotide-treated patients and 13.9–21.0% in placebo-treated patients.[17,18]

The secondary change-from-baseline endpoints help provide a more complete view of the potential clinical benefit of linaclotide compared with placebo, which may not be apparent from dichotomous responder endpoints alone. These endpoints demonstrated that linaclotide significantly improved bowel habits (CSBM/SBM frequency, stool consistency, and straining) and abdominal symptoms (abdominal pain, discomfort, and bloating) in IBS-C patients over 12 treatment weeks ($P < 0.0001$ for all endpoints). For each of these symptoms, differences between the treatment groups were seen within the first week and continued through week 12.

The overall incidence of TEAEs was notably lower in this predominantly Chinese population (30.3% of linaclotide-treated patients and 27.2% of placebo-treated patients) compared with the Phase 3 IBS-C trials conducted in North America (56.2–65.4% of linaclotide-treated patients and 53.0–56.6% of placebo-treated patients).[17,18] A similar pattern was noted in prucalopride trials of chronic constipation patients, where overall AE incidence was significantly higher in non-Asian women *versus* Asian women ($P < 0.001$).[24]

Consistent with linaclotide's pharmacology and previous linaclotide trials, diarrhea was the most commonly reported TEAE in this trial; however, incidence was lower in this trial than in the North American trials.[17,18] Diarrhea was generally mild to moderate in severity, and discontinuation rates due to diarrhea were low (<1%).

This trial provides valuable evidence regarding the efficacy and safety of linaclotide for IBS-C in a randomized controlled trial.[25] The findings, combined with previously published results from the Phase 3 IBS-C trials conducted in North America,[17–19] consistently demonstrated that 12 weeks of linaclotide treatment was associated with significant and sustained improvements in bowel habits, abdominal symptoms (including pain, discomfort, and bloating), and global measures in IBS-C patients. Linaclotide could potentially offer multi-symptom relief to IBS-C patients in China and other regions where available therapies do not adequately treat both the bowel and abdominal symptoms of IBS-C.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 Subgroup Analysis: Co-primary and Secondary Efficacy Endpoints by Geographic Region (ITT Population).

Table S2 Other Additional Efficacy Results During the 12-week Treatment Period (ITT Population).