

# Efficacy and safety of linaclotide in patients with irritable bowel syndrome with constipation: Chinese sub-cohort analysis of a phase III, randomized, double-blind, placebo-controlled trial

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**Objective:** To conduct a sub-cohort analysis to evaluate the efficacy and safety of linaclotide in Chinese patients with constipation-predominant irritable bowel syndrome (IBS-C) using data from a completed trial (NCT01880424).

**Methods:** In this phase III, double-blind, placebo-controlled trial, IBS-C patients were randomized to receive linaclotide (290 µg/d) or placebo for 12 weeks. Efficacy was assessed with two co-primary responder end-points (12-wk abdominal pain/discomfort: ≥30% reduction in either score with neither deteriorating from baseline for ≥6 wks; 12-wk IBS degree of relief: score ≤2 for ≥ 6 wks), seven secondary endpoints and several additional end-points.

**Results:** In total, 659 Chinese IBS-C patients received linaclotide (n = 327) or placebo (n = 332). The 12-week abdominal pain/discomfort end-point was met in 62.1% and 53.3% of the linaclotide-treated and placebo-treated patients, respectively (odds ratio [OR] 1.43, 95% confidence interval [CI] 1.05-1.96, *P* = 0.023); the 12-week IBS degree of relief end-point was achieved in 32.7% and 16.9% of the patients treated with linaclotide and placebo, respectively (OR 2.40, 95% CI 1.66-3.47, *P* < 0.001). The linaclotide-treated patients had a shorter time to the first spontaneous bowel movement than the placebo-treated patients (23.6 h vs 43.7 h, *P* < 0.001). Linaclotide produced significantly greater improvement than placebo in all secondary end-points from the first 2 weeks (all *P* < 0.001). Diarrhea was reported in 8.3% of linaclotide-treated patients and 1.2% of placebo-treated patients.

**Conclusion:** Linaclotide (290 µg/d) was efficacious and well-tolerated in Chinese IBS-C patients with a rapid onset of effect.

## KEYWORDS

abdominal pain, constipation, guanylate cyclase, irritable bowel syndrome, linaclotide

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## 1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain, discomfort and bloating that are associated with changes in bowel habits.<sup>1–4</sup> The underlying pathophysiology of IBS remains unclear, although several etiological factors, such as disordered gut–brain communication, visceral hypersensitivity, alterations in gastrointestinal motility, genetics, dysbiosis and psychosocial factors, have been identified.<sup>1,5,6</sup> According to the Rome diagnostic criteria, IBS is classified into four subtypes based on their symptomatology: constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), mixed-type IBS (IBS-M) and IBS-unclassified (IBS-U).<sup>4,7</sup> In particular, the characteristics of IBS-C include straining during bowel movements (BM), hard or lumpy stool, reduced frequency of BM and incomplete evacuation.<sup>1–3</sup>

In 2020, a large-scale study adopting the Rome III diagnostic criteria reported the prevalence rate of IBS in China to be 7.4% and 3.8%, respectively, based on an Internet Survey and a Household Survey.<sup>8</sup> In a nationwide cross-sectional study, the prevalence of IBS-C in all gastroenterology outpatients in China was 16.6%.<sup>9</sup> It has been estimated that only 25% of Chinese patients with IBS seek medical treatment from hospitals,<sup>4</sup> and more than half of them are not satisfied with the treatment outcome.<sup>10</sup> Although many medications for the treatment of IBS-C are available in China, they are not completely effective. For example, antispasmodics are primarily used to alleviate abdominal pain with limited effects on bowel symptoms,<sup>11</sup> whereas laxatives, bulking agents and lactulose are commonly used to alleviate constipation but are ineffective for or may even exacerbate abdominal symptoms.<sup>4,10</sup>

Linaclotide is a guanylate cyclase-C (GC-C) agonist and a 14-amino-acid polypeptide minimally absorbed in the gastrointestinal tract. Linaclotide binds to the GC-C receptors of the intestinal mucosa, resulting in an increased production of cyclic guanosine monophosphate (cGMP) followed by a greater fluid secretion into the intestine and eventually, an increased gastrointestinal motility and alleviation of constipation.<sup>12–15</sup> An increased cGMP level is also known to reduce the sensitivity of afferent nociceptors, thereby alleviating visceral hypersensitivity and abdominal pain.<sup>13–15</sup>

Several phase III clinical trials conducted in the North America have demonstrated the efficacy and safety of linaclotide in the treatment of IBS-C.<sup>16–18</sup> However, its efficacy and safety in the Chinese population with IBS-C have not yet been confirmed. Our previous study on the efficacy and safety of linaclotide on IBS-C has included patients from China;<sup>11</sup> however, dedicated analysis of the Chinese subgroup were not performed. In the current study, we aimed to analyze the efficacy and safety of linaclotide in the treatment of the Chinese sub-cohort with IBS-C.

## 2 | PATIENTS AND METHODS

### 2.1 | Trial design

This prespecified Chinese sub-cohort analysis was conducted based on our clinical trial which has been registered at ClinicalTrials.gov

(registration number NCT01880424), the methodology of which has been described in detail in our previous study.<sup>11</sup> In brief, this was a phase III, randomized, double-blind, placebo-controlled trial conducted at 40 clinical centers in China and 58 centers in North America and Oceania. In China the patients with IBS-C, either newly diagnosed or previously diagnosed, were enrolled from 31 July 2013 to 15 April 2015. The trial was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. The trial protocol was approved by the Ethics Committee of the Chinese PLA General Hospital (Beijing, China; approval number C2013-037-02) as well as the Ethics Committees of all other participating centers. Written informed consent was obtained from each patient before their enrollment.

All patients underwent screening during a time period of up to 21 days. Then the eligible patients were immediately included in the pretreatment period that lasted for 14–21 days. Bowel habits, symptoms and signs and their severity, and use of per-protocol rescue medicine or any other laxatives, suppositories or enema of the patients were recorded in an electronic diary (eDiary). Upon completing the pretreatment period, the patients proceeded to a randomly assigned treatment with either 290- $\mu$ g linaclotide or placebo for 12 weeks. The randomization algorithm was written by a statistician who was not otherwise involved in the trial. Patients were randomized centrally in blocks of eight in a 1:1 ratio to either treatment arm at each trial site. All patients were followed up for another 2 weeks post-treatment. They were asked to continue recording their symptoms in the eDiary throughout the treatment and post-treatment periods.

### 2.2 | Inclusion and exclusion criteria of the patients

The key inclusion criteria were: (a) adult patient  $\geq 18$  years of age; (b) fulfilled the Rome III criteria for IBS;<sup>19</sup> (c) with  $< 3$  BM per week and abdominal symptoms (straining, lumpy or hard stool, sensation of incomplete evacuation, etc) during over 25% of BM for  $\geq 3$  months before screening; (d) with  $\leq 5$  spontaneous bowel movements (SBM) per week,  $< 3$  complete spontaneous bowel movements (CSBM) per week, and with abdominal pain lasting for at least 2 days per week (scoring  $\geq 3.0$  out of 10 points on average on the numerical rating scale [NRS]) during the 2 weeks prior to randomization.<sup>11</sup>

The key exclusion criteria were: (a) loose or watery stool (Bristol Stool Form Scale [BSFS] score of 6–7) during over 25% of BM without taking any laxative, enema, suppository or prohibited medicine within 3 months prior to the screening; (b) BSFS score of 6 for over one SBM or 7 for any SBM during the 2 weeks prior to randomization; and (c) use of rescue medicine or any other laxative, enema, or suppository on the day of or 1 day before randomization.<sup>11</sup>

### 2.3 | Efficacy assessment and end-points

Efficacy was assessed based on patients' records in the eDiary. On a daily basis, patients recorded the severity of abdominal symptoms (all

on the NRS of 0-10, with 10 being the most severe), bowel habits including BM frequency and completeness (yes or no), stool consistency (BSFS score of 1-7), and degree of straining (on an ordinal scale of 1-5, with 5 being an extreme amount). On a weekly basis, patients reported degree of relief of IBS symptoms (on a balanced ordinal scale of 1-7, with 1 being “completely relieved”, 4 being “unchanged”, and 7 being “as bad as I can imagine”), severity of constipation and IBS symptoms severity (both on an ordinal scale of 1-5, with 5 being the most severe), adequacy of symptom relief (yes or no) and treatment satisfaction (on an ordinal scale of 1-5, with 5 being the most satisfied).

This sub-cohort analysis employed the same primary, secondary and additional end-points as in the primary analysis.<sup>11</sup> A patient who met the criterion for either end-point was defined as a responder.

### 2.3.1 | Co-primary end-points

The two co-primary efficacy end-points were: (a) the 12-week abdominal pain/discomfort end-point, defined as an improvement of  $\geq 30\%$  from baseline in either the mean weekly abdominal pain score or weekly abdominal discomfort score, without either score worsening from baseline, for at least 6 of the 12 weeks during the treatment period; and (b) the 12-week IBS degree of relief end-point, defined as a score of  $\leq 2$  in degree of relief of IBS symptoms within a week for at least 6 out of the 12 weeks during the treatment period.

### 2.3.2 | Secondary end-points

Seven secondary efficacy end-points were used to assess the changes in abdominal symptoms and bowel habits, namely the 12-week average changes from baseline in abdominal pain, abdominal discomfort, abdominal bloating, weekly CSBM frequency, weekly SBM frequency, stool consistency, and degree of straining.

### 2.3.3 | Additional end-points

Several additional efficacy end-points were employed to evaluate the robustness of results, including: (a) the weekly average changes from baseline in the seven secondary efficacy end-points; (b) 12-week treatment satisfaction; (c) median time to the first SBM; (d) the percentage of patients experiencing an SBM within 24 hours after the first dose of the medication; (e) the percentage of patients experiencing a CSBM within 24 hours after the first dose; (f) sustained abdominal pain/discomfort and sustained IBS degree of relief end-points, defined as having achieved the respective co-primary end-points and being a weekly responder for at least 2 out of the 4 weeks before treatment completion; (g) 9-week/12-week average change from baseline in CSBM ( $\geq 3$  per week with  $\geq 1$  increase from baseline for at least 9 weeks); (h) 9-week/12-week average change from baseline in abdominal pain ( $\geq 30\%$  improvement from baseline for at least 9 weeks);

(i) 12-week combined CSBM/abdominal pain end-point ( $\geq 1$  increase in CSBM from baseline and  $\geq 30\%$  improvement from baseline in abdominal pain for  $\geq 6$  weeks, in accordance with the most up-to-date recommendations from the U.S. Food and Drug Administration [FDA]<sup>20</sup> and European Medicines Agency [EMA]<sup>21</sup>); (j) 9-week/12-week combined CSBM/abdominal pain end-point ( $\geq 1$  increase in CSBM from baseline and  $\geq 30\%$  improvement from baseline in abdominal pain for at least 9 weeks); (k) 12-week abdominal pain, discomfort and bloating responder end-points ( $\geq 30\%$  improvement from baseline for at least 6 weeks); (l) incremental 12-week CSBM responder end-point (an increase of  $>0$  to  $\geq 7$  from baseline at an interval of one in 12-week CSBM frequency); (m) incremental 12-week abdominal pain responder end-point (an improvement of  $>0\%$  to  $\geq 70\%$  from baseline at an interval of 10% in 12-week abdominal pain); (n) incremental 12-week abdominal discomfort responder end-point (an improvement of  $>0\%$  to  $\geq 70\%$  from baseline at an interval of 10% in 12-week abdominal discomfort); (o) 12-week mean change from baseline in abdominal cramping, abdominal fullness, IBS severity and constipation severity; (p) IBS symptom severity end-point (decrease by  $\geq 1$  from baseline for at least 6 weeks); (q) constipation severity end-point (decrease by  $\geq 1$  from baseline for at least 6 weeks); and (r) adequate relief of IBS symptoms end-point ( $\geq 6$  weeks).

### 2.3.4 | Subgroup analysis

Prespecified subgroup analyses for the co-primary and secondary end-points were performed based on patients' sex (female or male), age group ( $<65$  y or  $\geq 65$  y), body mass index (BMI) ( $<30$  kg/m<sup>2</sup> or  $\geq 30$  kg/m<sup>2</sup>), and baseline abdominal pain (NRS  $<5$ ,  $\geq 5$  and  $<8$ , and  $\geq 8$ ).

## 2.4 | Safety assessment

Patients reported any adverse events (AE) at study visits. The severity of the AE and their relationship with the study drug were subsequently evaluated by the investigators. Other items that were assessed at each visit included clinical laboratory parameters, vital signs and physical conditions of the patients.

## 2.5 | Statistical analysis

It was planned that approximately 80% of the total global participants would be enrolled in China, which was assumed to be around 640 Chinese patients. Based on the results of a previous North American phase III clinical trial assessing the efficacy and safety of linaclotide in patients with IBS-C,<sup>17</sup> it was assumed that such a sample size of the China region alone had more than 80% statistical power to discern any differences between the linaclotide and placebo groups for the co-primary end-points.

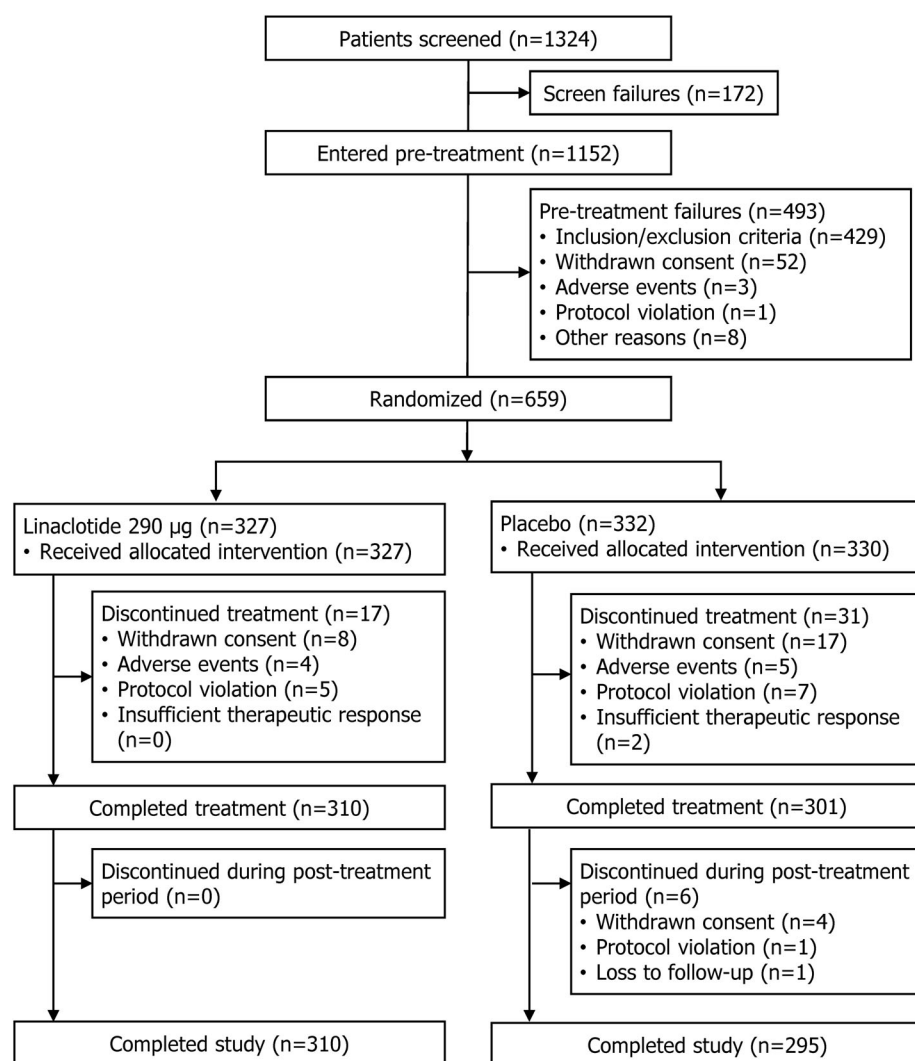
All the statistical analyses were conducted using the SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) for Windows. By employing a

three-step serial gatekeeping multiple comparison procedure (MCP), the overall family-wise type I error rate was controlled at a significance level of 0.05 for testing the co-primary and secondary efficacy end-points. The MCP required that the testing of statistical significance could proceed to the next step only if all individual null hypotheses within the current step were rejected at a step-specific overall significance level of 0.05. The first step of the MCP tested the two co-primary efficacy parameters, and both *P* values had to be less than 0.05 to be considered as meeting the primary efficacy objective. The second step tested the four secondary parameters on bowel symptoms (weekly CSBM frequency, weekly SBM frequency, stool consistency and degree of straining) with an overall type I error rate of 0.05 by means of the Hochberg procedure to control for multiple parameters within the step.<sup>22</sup> The third step tested the three secondary efficacy parameters on abdominal symptoms (abdominal pain, discomfort and bloating), also with an overall type I error rate of 0.05 by means of the Hochberg procedure.<sup>22</sup> For each of the primary and secondary efficacy parameters, the result was considered statistically significant only if the corresponding MCP criteria were met. For the additional

efficacy end-points and subgroup analyses, type I error was not controlled and therefore, *P* values should be considered nominal without adjustment for multiplicity. All statistical tests conducted were two-sided. An intention-to-treat (ITT) approach was adopted for all efficacy analyses. Safety analyses were entirely descriptive and were conducted in the safety population, defined as all patients who received the study drug at least once.

For each responder end-point, the proportion of responders in the linaclotide group was compared with that in the placebo group through the Cochran-Mantel-Haenszel (CMH) test. Statistically significant improvement using linaclotide compared with that using placebo was required for both co-primary efficacy end-points to meet the primary efficacy objective.

For all parameters of the change from baseline type, the linaclotide group was compared with the placebo group using an analysis of covariance (ANCOVA) model. All least-squares means reported were derived from ANCOVA. Treatment satisfaction was analyzed using an analysis of variance (ANOVA) model. A survival analysis for each group was conducted to determine the time to first SBM and a log-rank test was used for comparisons.



**FIGURE 1** Flowchart of patient recruitment and randomization

**TABLE 1** Baseline characteristics of the patients

Variables	Linacotide (n = 327)	Placebo (n = 332)	Overall (n = 659)	P value <sup>a</sup>
Age, years (mean ± SD)	39.6 ± 12.8	40.5 ± 13.9	40.1 ± 13.3	0.425
Age <65 y, n (%)	316 (96.6)	318 (95.8)	634 (96.2)	0.567
Female sex, n (%)	264 (80.7)	287 (86.4)	551 (83.6)	0.048
Height, cm (mean ± SD)	163.0 ± 6.3	162.0 ± 6.5	162.5 ± 6.4	0.037
Weight, kg (mean ± SD)	58.2 ± 9.5	58.0 ± 9.2	58.1 ± 9.3	0.773
BMI, kg/m <sup>2</sup> (mean ± SD)	21.8 ± 2.8	22.1 ± 2.9	22.0 ± 2.8	0.339
Weekly CSBM count (mean ± SD)	0.3 ± 0.6	0.3 ± 0.5	0.3 ± 0.5	0.201
Weekly SBM count (mean ± SD)	1.7 ± 1.2	1.6 ± 1.2	1.7 ± 1.2	0.272
Stool consistency evaluated by BSFS <sup>b</sup> (mean ± SD)	2.8 ± 1.1	2.6 ± 1.2	2.7 ± 1.1	0.095
Degree of straining <sup>b</sup> (mean ± SD)	3.1 ± 0.9	3.2 ± 0.9	3.1 ± 0.9	0.283
Abdominal bloating score (mean ± SD)	5.1 ± 1.8	5.3 ± 1.7	5.2 ± 1.8	0.440
Abdominal pain score (mean ± SD)	4.8 ± 1.4	4.9 ± 1.3	4.9 ± 1.3	0.589
Abdominal discomfort score (mean ± SD)	5.0 ± 1.5	5.0 ± 1.5	5.0 ± 1.5	0.688

Abbreviations: BMI, body mass index; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movements; SBM, spontaneous bowel movements; SD, standard deviation.

Note: all baseline efficacy-related characteristics were calculated based on patient data from the eDiaries during the 14 days prior to randomization.

<sup>a</sup>All categorical variables were tested using the Cochran-Mantel-Haenszel test; all continuous variables were tested using ANOVA.

<sup>b</sup>Only 579 patients had data on stool consistency and degree of straining (292 in the linacotide group; 287 in the placebo group).

**TABLE 2** Co-primary and secondary efficacy end-points

Efficacy end-points	Linacotide (n = 327)	Placebo (n = 332)	P value <sup>a</sup>
Co-primary end-points, n (%)			
12-week abdominal pain/abdominal discomfort: ≥30% improvement from baseline in mean weekly abdominal pain or discomfort score without either one deteriorating from baseline in that week for ≥6 weeks	203 (62.1)	177 (53.3)	0.023
12-week IBS degree of relief: “considerable” or “complete” relief of IBS symptoms in a week for ≥6 weeks	107 (32.7)	56 (16.9)	<0.001
Secondary end-points			
12-week change from baseline (mean ± SEM)			
Weekly CSBM count	1.657 ± 0.096	0.893 ± 0.096	<0.001
Weekly SBM count	2.556 ± 0.113	1.341 ± 0.112	<0.001
Stool consistency (BSFS)	1.539 ± 0.052	0.872 ± 0.053	<0.001
Degree of straining	−1.222 ± 0.037	−0.908 ± 0.037	<0.001
Abdominal bloating score	−1.689 ± 0.088	−1.182 ± 0.087	<0.001
Abdominal pain score	−1.864 ± 0.085	−1.415 ± 0.084	<0.001
Abdominal discomfort score	−1.664 ± 0.083	−1.264 ± 0.083	<0.001

Abbreviations: BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movements; IBS, irritable bowel syndrome; SBM, spontaneous bowel movements; SEM, standard error of mean.

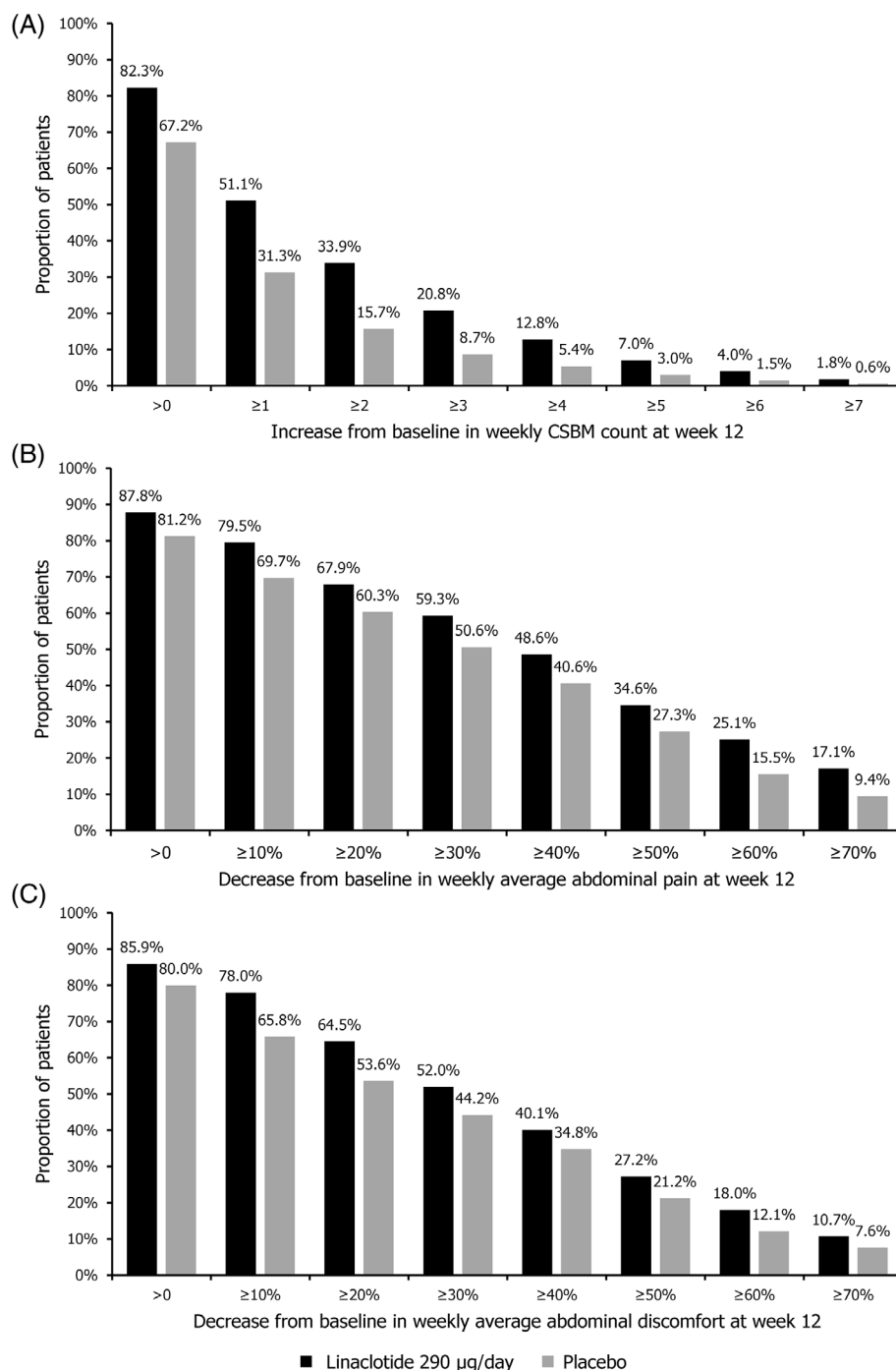
<sup>a</sup>All co-primary end-points were tested using the Cochran-Mantel-Haenszel test; all secondary end-points were tested using ANCOVA.

### 3 | RESULTS

#### 3.1 | Study population

Of the 1324 Chinese patients screened, 1152 entered the pre-treatment period and 659 of them were randomized to receive either

linacotide (n = 327) or placebo (n = 332). Finally, 310 (94.8%) and 301 (90.7%) patients from the linacotide group and the placebo group, respectively, completed the 12-week treatment. Additionally, 310 (94.8%) and 295 (88.9%) patients from the linacotide and placebo groups, respectively, completed the post-treatment follow-up (Figure 1). The mean age of all patients was 40.1 years and the overall



**FIGURE 2** A, Incremental 12-week complete spontaneous bowel movement (CSBM) responder end-point.  $P < 0.05$  at each level of increase, except for an increase of  $\geq 6$  ( $P = 0.052$ ) and  $\geq 7$  ( $P = 0.149$ ). B, Incremental 12-week abdominal pain responder end-point.  $P < 0.05$  at each level of increase. C, Incremental 12-week abdominal discomfort responder end-point.  $P < 0.05$  at each level of increase, except for an increase of  $\geq 40\%$  ( $P = 0.168$ ),  $\geq 50\%$  ( $P = 0.073$ ) and  $\geq 70\%$  ( $P = 0.164$ ). Statistical analysis was performed using the Cochran-Mantel-Haenszel test. ■ Linacotide 290 µg/d; ■ placebo

proportion of women was 83.6%. As shown in Table 1, the patients' characteristics between the two groups were similar except for the female sex and height; the linacotide group had a lower proportion of women (80.7% vs 86.4%,  $P = 0.048$ ) and a greater height (163.0 vs 162.0 cm,  $P = 0.037$ ) than the placebo group.

### 3.2 | Efficacy

Altogether 62.1% (203/327) of the patients in the linacotide group reached the 12-week abdominal pain/discomfort end-point was,

which was significantly higher than 53.3% (177/332) of the placebo group (odds ratio [OR] 1.43, 95% confidence interval [CI] 1.05-1.96,  $P = 0.023$ ) (Table 2). Similarly, 32.7% (107/327) of the linacotide group achieved the 12-week IBS degree of relief end-point compared with 16.9% (56/332) in the placebo group (OR 2.40, 95% CI 1.66-3.47,  $P < 0.001$ ) (Table 2).

For all seven secondary efficacy end-points, the linacotide group showed significantly greater improvement than the placebo group (all  $P < 0.001$ ; Table 2). These results indicated that compared with the placebo, linacotide achieved statistically significant improvements for both co-primary end-points and all secondary end-points.



**TABLE 3** Subgroup analysis by patients' sex

Efficacy end-points	Female			Male		
	Linacotide (n = 264)	Placebo (n = 287)	P value <sup>a</sup>	Linacotide (n = 63)	Placebo (n = 45)	P value <sup>a</sup>
Co-primary end-points, n (%)						
12-week abdominal pain/abdominal discomfort	163 (61.7)	160 (55.7)	0.154	40 (63.5)	17 (37.8)	0.009
12-week IBS degree of relief	87 (33.0)	50 (17.4)	<0.001	20 (31.7)	6 (13.3)	0.028
Secondary end-points						
12-week change from baseline (mean ± SEM)						
Weekly CSBM count	1.595 ± 0.104	0.886 ± 0.100	<0.001	1.916 ± 0.248	0.935 ± 0.293	0.012
Weekly SBM count	2.563 ± 0.125	1.261 ± 0.120	<0.001	2.529 ± 0.263	1.845 ± 0.311	0.096
Stool consistency (BSFS)	1.561 ± 0.057	0.883 ± 0.056	<0.001	1.429 ± 0.125	0.810 ± 0.149	0.002
Degree of straining	−1.213 ± 0.040	−0.934 ± 0.040	<0.001	−1.260 ± 0.089	−0.734 ± 0.106	<0.001
Abdominal bloating score	−1.717 ± 0.098	−1.236 ± 0.094	<0.001	−1.544 ± 0.199	−0.883 ± 0.236	0.035
Abdominal pain score	−1.889 ± 0.094	−1.464 ± 0.091	0.001	−1.756 ± 0.190	−1.113 ± 0.225	0.031
Abdominal discomfort score	−1.701 ± 0.093	−1.315 ± 0.090	0.003	−1.484 ± 0.178	−0.979 ± 0.211	0.070

Note: 12-week abdominal pain/discomfort, defined as ≥30% improvement from baseline in mean weekly abdominal pain or discomfort score without either one deteriorating from baseline in that week for at least 6 weeks; 12-week irritable bowel syndrome (IBS) degree of relief, defined as “considerable” or “complete” relief of IBS symptoms in a week for at least 6 weeks.

Abbreviations: BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movements; SBM, spontaneous bowel movements; SEM, standard error of mean.

<sup>a</sup>All co-primary end-points were tested using the Cochran-Mantel-Haenszel test; all secondary end-points were tested using the analysis of covariance.

Analyses of additional efficacy end-points showed that more patients treated with linacotide experienced their first SBM within 24 hours after the first dose compared with the placebo group (51.4% [168/327] vs 30.4% [101/332],  $P < 0.001$ ; Table S1). The linacotide group experienced a much shorter time to the first SBM than the placebo group after the first dose (23.60 h vs 43.74 h,  $P < 0.001$ ; Table S1). The proportion of patients who had the first CSBM within 24 hours after the first dose was also higher in the linacotide group than in the placebo group (16.8% [55/327] vs 6.9% [32/332],  $P < 0.001$ ; Table S1).

For all secondary efficacy parameters as well as weekly average treatment satisfaction, the linacotide group achieved greater improvements than the placebo group, starting from the first or second week after treatment initiation (Figure S1). The differential responses between the linacotide group and the placebo group were sustained for the rest of the treatment period, as continuous improvements were observed in the linacotide group for all parameters throughout the treatment period (Figure S1). For nearly all other additional efficacy endpoints, the linacotide group also tended to improve more significantly than the placebo group (Table S1). Particularly, for the 12-week CSBM/abdominal pain end-point, also referred to as the FDA end-point (in previous North American trials<sup>16,18</sup>) or the EMA end-point, the proportion of responders in the linacotide group (35.2% [115/327]) was higher than that in the placebo group (22.3% [74/332]) (OR 1.89, 95% CI 1.34–2.67,  $P < 0.001$ ) (Table S1).

For every incremental responder end-point, the proportions of responders in both the linacotide and placebo groups decreased with the use of more stringent responder thresholds (Figure 2). For the

incremental 12-week CSBM end-point, a greater proportion of patients with a defined increase from baseline in weekly CSBM at week 12 were observed in the linacotide group than in the placebo group at each incremental level of increase ( $P < 0.05$ ), except for increases of ≥6 ( $P = 0.052$ ) and ≥7 ( $P = 0.149$ ) (Figure 2A). Similarly, for the incremental abdominal pain and discomfort responder end-points, linacotide achieved improvements from baseline in more patients regardless of incremental levels (all  $P < 0.05$ , except for the improvements of ≥40%, ≥50% and ≥70% for abdominal discomfort) (Figure 2B,C).

For the subgroup analyses, the linacotide group achieved greater efficacy than the placebo group for most co-primary and secondary end-points, regardless of patients' sex, age, BMI and baseline abdominal pain score. Some subgroups appeared to achieve better responses, although the differences between the subgroups were not statistically evaluated.

The results of subgroup analysis according to the patient's sex are presented in Table 3. For the 12-week abdominal pain/discomfort end-point, the proportion of responders in the linacotide group was marginally higher than that in the placebo group for the female subgroup (61.7% [163/264] vs 55.7% [160/287],  $P = 0.154$ ), but it was substantially greater in the linacotide group than in the placebo group for the male subgroup (63.5% [40/63] vs 37.8% [17/45],  $P = 0.009$ ). For the 12-week IBS degree of relief end-point, higher proportions of responders were observed in linacotide-treated patients for both male and female subgroups ( $P < 0.001$  and  $P = 0.028$ , respectively). Notable improvements in the linacotide group compared with the placebo group were observed in almost all secondary end-point parameters for both subgroups.





**TABLE 5** Summary of adverse events (AE)

n (%)	Linacotide (n = 327)	Placebo (n = 330)
Patients with any TEAE	91 (27.8)	89 (27.0)
Common TEAE <sup>a</sup>		
Diarrhea	27 (8.3)	4 (1.2)
Mild	17 (5.2)	3 (0.9)
Moderate	10 (3.1)	1 (0.3)
Severe	0 (0)	0 (0)
Upper respiratory tract infection	17 (5.2)	20 (6.1)
Increased ALT level	6 (1.8)	6 (1.8)
Nasopharyngitis	2 (0.6)	4 (1.2)
Abdominal pain	3 (0.9)	5 (1.5)
Back pain	5 (1.5)	1 (0.3)
Upper abdominal pain	4 (1.2)	1 (0.3)
Anemia	2 (0.6)	4 (1.2)
Death	0 (0)	0 (0)
Patients with any SAE	3 (0.9)	8 (2.4)
Patients with any severe TEAE	3 (0.9)	7 (2.1)
AE leading to discontinuation of the medication	6 (1.8)	8 (2.4)

Abbreviations: ALT, alanine aminotransferase; SAE, serious adverse events; TEAE, treatment-emergent adverse events.

<sup>a</sup>TEAE occurring in  $\geq 1.0\%$  of patients in either group.

The results of subgroup analyses according to baseline abdominal pain score are shown in Table 4. For the 12-week abdominal pain/discomfort end-point, in the subgroup of NRS  $<5$  the proportion of responders in the linacotide group was slightly higher than in the placebo group (57.1% [113/198] vs 51.2% [103/201],  $P = 0.243$ ); whereas in the NRS  $\geq 5$  and  $<8$  subgroups, more patients in the linacotide group achieved the end-point compared with the placebo group (70.0% [84/120] vs 58.1% [72/124],  $P = 0.053$ ). For the 12-week IBS degree of relief end-point, higher proportions of responders were observed in linacotide-treated patients for both subgroups (both  $P < 0.05$ ). For all secondary efficacy parameters, linacotide-treated patients in both subgroups showed greater improvement than the placebo group.

Due to the small numbers of subjects in the subgroup aged  $>65$  years and the subgroup of BMI  $>30$  kg/m<sup>2</sup>, the results of subgroup analyses based on age and BMI might carry little significance compared with the Chinese sub-cohort analysis and are thus presented in Tables S2 and S3, respectively.

### 3.3 | Safety

All together 657 patients were enrolled in the evaluation of safety of linacotide, including 327 in the linacotide group and 330 in the placebo group. Treatment-emergent adverse events (TEAE) occurred in 27.8% (91/327) and 27.0% (89/330) of patients in the linacotide and

the placebo groups, respectively (Table 5). The majority of the TEAE were mild or moderate.

The most common TEAE in the linacotide group was diarrhea, as reported by 8.3% (27/327) of the patients, while 1.2% (4/330) of the placebo group reported diarrhea (Table 5). All cases of diarrhea in both groups were mild or moderate in nature. One patient (0.3%) in each group discontinued treatment due to diarrhea, with the case in the linacotide group being moderate in severity and that in the placebo group being mild.

The median time to the first episode of diarrhea was 15.0 days for the linacotide group and 27.5 days for the placebo group (Table S4). Four (14.8%) of the linacotide-treated patients with diarrhea experienced the onset of diarrhea on day 1, compared with none in the placebo group (Table S5). In the linacotide group, 33.3% (9/27) of patients with diarrhea had the first episode of diarrhea by week 1 of treatment, 66.7% (18/27) by week 4 of treatment, and 88.9% (24/27) by week 6 of treatment (Table S5).

Serious AE (SAE) occurred in 0.9% (3/327) and 2.4% (8/330) of the patients in the linacotide and placebo groups, respectively (Table 5). The SAE reported in the linacotide group included induced abortion, ectopic pregnancy (which led to discontinuation of the medication) and pericoronitis. The SAE reported in the placebo group included induced abortion in three cases, spontaneous abortion, bladder outlet obstruction, colitis, multiple system atrophy (which led to discontinuation of the medication) and uterine leiomyoma in one patient each. All SAE were assessed by investigators and were found to be unrelated to the use of linacotide or placebo, except for the one case of spontaneous abortion in the placebo group. No death occurred in either group. The two groups showed no clinically significant disparities in laboratory abnormalities, vital signs or electrocardiogram parameters.

## 4 | DISCUSSION

To our knowledge, this is the first dataset from a phase-III-trial setting that demonstrated the efficacy and safety of linacotide in treating IBS-C in a patient population of only Chinese adults. The results from this Chinese sub-cohort were consistent with those from previous North American trials and a recent Japanese trial.<sup>16–18,23</sup> This sub-cohort analysis supports the efficacy of linacotide in meeting the clinical needs of Chinese patients with IBS-C, as linacotide alleviates constipation, an effect that is scarcely achievable by antispasmodics which mainly target abdominal pain,<sup>11</sup> and relieves abdominal symptoms that cannot be satisfactorily addressed by laxatives, bulking agents or lactulose.<sup>4,10</sup> In January 2019, linacotide (290 µg once daily) was approved by the National Medical Products Administration of China for the treatment of IBS-C and it is the only drug indicated for IBS-C in China.

A single-center, prospective cohort study estimated that IBS-C could incur substantial direct medical costs (including costs for diagnostics, treatment and care) of RMB 12 036.72/person-years in China.<sup>24</sup> The Chinese sub-cohort analysis in this study provides

evidence of the clinical benefits of linaclotide in treating Chinese patients with IBS-C, and could serve as the basis for future pharmacoeconomic analysis on linaclotide in China.

The parent trial of this sub-cohort analysis included 659 (78.5%) Chinese, 41 (4.9%) Oceanian and 139 (16.6%) North American patients, respectively.<sup>11</sup> Patients treated with linaclotide in all the three sub-cohorts achieved the two co-primary efficacy end-points (except for the North American sub-cohort, which did not achieve a significant improvement in the 12-week abdominal pain/discomfort end-point), with a higher proportion of Chinese patients achieving the respective co-primary end-points than their counterpart sub-cohorts (12-week abdominal pain/discomfort end-point: 62.1% vs 52.2%; 12-week IBS degree of relief end-point: 32.7% vs 26.9%–30.4%). Yet it is worth noting that the Chinese sub-cohort also had the highest proportion of placebo responders (12-week abdominal pain/discomfort end-point: 53.3% vs 16.7%–36.1%; 12-week IBS degree of relief end-point: 16.9% vs 5.6%–11.1%).

Compared with previous North American trials,<sup>17</sup> this Chinese sub-cohort exhibited a similar level of linaclotide efficacy. The linaclotide group in the Chinese sub-cohort had a greater proportion of 12-week abdominal pain/discomfort responders (62.1% vs 54.1% or 54.8%), but also a higher proportion of responders in the placebo group (53.3% vs 38.5% or 41.8%). In terms of 12-week IBS degree of relief, the Chinese sub-cohort had a slightly lower proportion of responders in the linaclotide group (32.7% vs 37.0% or 39.4%) but a similar placebo response rate (16.9% vs 16.6% or 18.5%) as in previous North American trials.<sup>17</sup> As for the FDA end-point, the Chinese sub-cohort had a similar proportion of responders in both the linaclotide and placebo groups compared with previous North American trials (linaclotide: 35.2% vs 33.6% or 33.7%; placebo: 22.3% vs 13.9% or 21.0%).<sup>16,18</sup>

Response rates to placebo are known to be high among randomized clinical trials conducted in IBS patients.<sup>25</sup> This might be attributed to various factors, such as patients' expectations of drug efficacy, variations in their psychiatric states and the definition of end-points (where an improvement threshold of 30% for abdominal pain/discomfort might permit a high placebo response rate).<sup>25,26</sup> Yet the observed placebo response was considerably greater in the Chinese sub-cohort compared with the previous North American trials, especially for the 12-week abdominal pain/discomfort end-point. Interestingly, the Chinese sub-cohort had lower disease severity at baseline, as characterized by a lower abdominal pain/discomfort score, together with a higher weekly CSBM/SBM frequency.<sup>16,18</sup> A lower disease severity at baseline suggests better neuropsychiatric conditions and a shorter disease history in patients, both of which are associated with greater placebo effects.<sup>27,28</sup> Nevertheless, when using other end-points including the 12-week IBS degree of relief end-point and the FDA end-point, the extent of placebo responses in the Chinese sub-cohort was reduced considerably and became comparable with previous trials.<sup>16–18</sup> Stricter definitions of end-points could also reduce placebo response, as exemplified by the incremental responder end-points (Figure 2). Therefore, to reduce the placebo response in future trials to be conducted in Chinese IBS-C patients, it may be

worthwhile to increase the improvement thresholds for abdominal pain/discomfort to 40%, even 50%, when defining the two co-primary end-points, especially the 12-week abdominal pain/discomfort end-point.

The results of this Chinese sub-cohort analysis also demonstrate the fast onset of effect that could be achieved by linaclotide, a feature that has not been extensively reported in previous North American trials.<sup>16–18</sup> The proportions of patients experiencing SBM or CSBM within 24 hours after the first dose were considerably higher in the linaclotide group than in the placebo group. Moreover, a shorter time was needed by the linaclotide group to reach SBM after the first dose compared with the placebo group. The linaclotide group experienced a greater alleviation of constipation (higher SBM/CSBM frequency, higher stool consistency score and lower degree of straining) than the placebo group starting from the first week of treatment, with the maximal alleviation achieved at weeks 9–11. Regarding abdominal symptoms, the linaclotide group also showed a greater degree of relief (decreased severity of abdominal pain, discomfort and bloating) compared with the placebo group from as early as the first 1–2 weeks after treatment initiation, with progressive relief throughout the 12-week treatment. These improvements achieved by linaclotide over placebo were maintained throughout the treatment period.

In clinical trial settings, linaclotide showed similar response trends to the most recent secretagogues such as plecanatide (another GC-C agonist) and tenapanor (an inhibitor of the sodium/hydrogen exchanger 3).<sup>29,30</sup> Compared with previous IBS medications such as lubiprostone (a chloride channel activator) and tegaserod (a 5-hydroxytryptamine type 4 receptor agonist), linaclotide achieved somewhat faster improvements in abdominal symptoms.<sup>31,32</sup> In two clinical trials, for IBS-C patients, lubiprostone (8 mcg twice daily) required 1 month of treatment before showing a significant improvement from baseline in abdominal pain/discomfort compared to the placebo,<sup>31</sup> while tegaserod (6 mg twice daily) required 2 weeks before showing such an effect.<sup>32</sup> Nevertheless, the response trends in constipation-related symptoms were similar among linaclotide and the two said IBS medications.<sup>31,32</sup>

Subgroup analyses revealed that the efficacy of linaclotide in most subgroups was consistent with that of the full sub-cohort. Between the male and female subgroups, the proportions of responders for both co-primary end-points were similar, but for the 12-week abdominal pain/discomfort end-point, the female subgroup had a higher response rate to placebo than the male subgroup (55.7% vs 37.8%), suggesting a larger treatment effect in the male subgroup than in the female subgroup (difference in response rate between placebo and linaclotide: 25.7% vs 6.0%). For the subgroup analysis based on baseline abdominal pain score, the proportion of responders for the 12-week abdominal pain/discomfort end-point was higher in patients with moderate abdominal pain than in those with mild abdominal pain (NRS  $\geq 5$  and  $< 8$  vs NRS  $< 5$ : 70.0% vs 57.1%), with a larger treatment effect in the former subgroup (difference in response rate between linaclotide and placebo: 11.9% vs 5.8%) as the two subgroups had similar response rates to placebo. It should be noted that the differences between subgroups may not possess significance as they were not statistically evaluated, and that some of the variations

in efficacy results are due to less subjects in the subgroups. Nevertheless, results of the subgroup analyses indicated that male sex and greater baseline abdominal pain are probably associated with better response for the 12-week abdominal pain/discomfort end-point. But other end-points assessing different aspects of IBS-C symptoms should always be employed to assess efficacy holistically.

In terms of safety, the Chinese sub-cohort in this study had lower rates of TEAE than previous North American trials (linaclotide: 27.8% vs 56.2% or 65.4%; placebo: 27.0% vs 53.0% or 56.6%),<sup>16,18</sup> and similar rates compared to the Japanese trial (31.3% and 25.9% in linaclotide and placebo groups, respectively).<sup>23</sup> The most common TEAE reported in the Chinese sub-cohort was diarrhea, which was consistent with previous North American trials.<sup>16,18</sup> However, diarrhea was much less frequent in both linaclotide and placebo groups of the Chinese sub-cohort compared with their North American counterparts (linaclotide: 8.3% vs 19.5% or 19.7%; placebo: 1.2% vs 2.5% or 3.5%).<sup>16,18</sup> These findings suggest that linaclotide may be better tolerated in Chinese patients than in North American patients. Furthermore, this study is the first to report the time to the first treatment-emergent diarrhea (defined as diarrhea that occurred during the treatment period) and the detailed time distribution of these cases with diarrhea. It was observed that the first diarrheal episode most likely occurred at the early stage of treatment (the first 4 wks), and that new diarrheal cases started to become rare after 6 weeks of treatment. Therefore, it is advisable to follow up patients with IBS-C proactively during the early stage of linaclotide treatment so that treatment-emergent diarrhea may be addressed promptly. The frequency of follow-up may be reduced once the patient's stool pattern has become stable.

A major limitation of the study was that the long-term efficacy and safety profiles of linaclotide could not be determined due to the relatively short treatment period of 12 weeks. Such profiles are necessary, as long-term treatment may be needed in patients with IBS to achieve sustained alleviation of symptoms.

## 5 | CONCLUSIONS

Linaclotide showed good efficacy and safety in the treatment of Chinese adult patients with IBS-C. Therapy with linaclotide brought about adequate improvement of the whole spectrum of IBS-C symptoms starting from 2 weeks after treatment initiation. A higher proportion of Chinese linaclotide-treated patients achieved the 12-week abdominal pain/discomfort end-point than the other sub-cohorts of the parent study, but the corresponding placebo response rate in the Chinese sub-cohort was also higher, especially in the female subgroup. In future clinical trials involving Chinese patients with IBS-C, more stringent criteria to define the 12-week abdominal pain/discomfort end-point may be needed to reduce placebo response.

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## CONFLICT OF INTEREST

None.

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## SUPPORTING INFORMATION

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