A novel score to evaluate abdominal symptom improvement in patients with constipation-predominant irritable bowel syndrome demonstrates efficacy of linaclotide for improving abdominal bloating, discomfort, and pain in a Phase 3b trial

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INTRODUCTION

- The Diary for Irritable Bowel Syndrome Symptoms-Constipation (DIBSS-C) is a new patient-reported outcome measure of bowel and abdominal symptoms
  - The DIBSS-C was developed by the Irritable Bowel Syndrome (IBS) Working Group of the Critical Path Institute's Patient-Reported Outcome Consortium for use in IBS with constipation (IBS-C) clinical trials[1]
- A multi-item Abdominal Score was derived from the three abdominal symptom items of the DIBSS-C (abdominal bloating, abdominal discomfort, and abdominal pain)[2,3] [**Figure 1**]
- Linaclotide is a guanylate cyclase-C (GC-C) agonist approved for treating IBS-C, as well as chronic idiopathic constipation, in adults
- The present study, evaluating linaclotide in IBS-C, is the first use of the Abdominal Score to evaluate treatment efficacy in a randomized, double-blind, placebo-controlled, Phase 3 study

Figure 1. Definition of the Abdominal Score

Abdominal Score is a multi-component primary efficacy endpoint

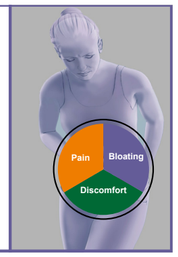
- **Pain:** Worst **abdominal pain** over the past 24 hours
- **Bloating:** Worst **abdominal bloating** over the past 24 hours
- **Discomfort:** Worst **abdominal discomfort** over the past 24 hours

Daily eDiary reports on an 11-point NRS, where:

- 0 = "No"
- 10 = "Worst"

0 1 2 3 4 5 6 7 8 9 10

- *Abdominal Score* is the average of the three components (Pain + Bloating + Discomfort)/3



NRS, numerical rating scale.

OBJECTIVE

- The objective of the present study was to evaluate treatment efficacy in a randomized, double-blind, placebo-controlled, Phase 3 study of linaclotide in IBS-C using the Abdominal Score

METHODS

- Patients with IBS-C and a baseline abdominal pain score of ⩾3 (0–10-point scale; 0=none, 10=worst possible abdominal pain) were randomized to linaclotide 290 μg or placebo daily for 12 weeks, followed by a 4-week randomized withdrawal period
- Daily Abdominal Score was calculated as the average of the daily abdominal bloating, abdominal discomfort, and abdominal pain assessments (all assessed on a 0–10-point scale; as above)
  - Weekly Abdominal Score was the average of the available daily Abdominal Scores in a week
- The primary endpoint was a change from baseline in Abdominal Score for the overall treatment period
  - Analyzed at each week over 12 weeks, using a mixed model with repeated measures
- The secondary endpoints were:
  - Change from baseline in 12-week Abdominal Score (evaluated using empirical cumulative distribution function)
  - 6/12-week Abdominal Score responder rate, calculated as an at least 2-point improvement in the weekly Abdominal Score for ⩾6/12 weeks, based on previously reported psychometric analyses in IBS-C[2,3]
- Primary and secondary endpoints were controlled for multiplicity
- Additional endpoints included change from baseline in individual abdominal symptoms
- Adverse events (AEs) were monitored throughout the study

RESULTS

Patient Demographics and Baseline Characteristics

- Overall, 614 patients were randomized (placebo: n=308; linaclotide: n=306)
  - All were included in the intent-to-treat and safety populations
- Treatment groups were well balanced with respect to demographics and baseline characteristics (**Table 1**)

Table 1. Patient demographics and baseline characteristics

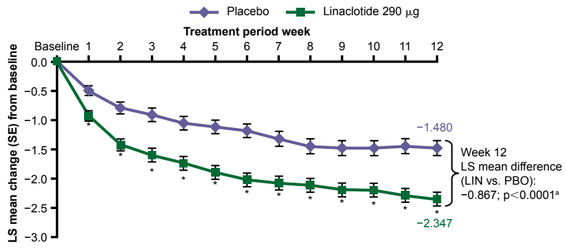
Characteristics	Placebo (n=308)	Linaclotide (n=306)
Age (years), mean (range)	46.8 (18, 79)	46.5 (19, 85)
⩾65 years, n (%)	36 (11.7)	33 (10.8)
Female, n (%)	255 (82.8)	241 (78.8)
Race, n (%)		
White	198 (64.3)	189 (61.8)
Black	70 (22.7)	76 (24.8)
Asian	35 (11.4)	36 (11.8)
Other	5 (1.6)	5 (1.6)
Body mass index, mean (SD)	29.39 (6.51)	29.50 (6.88)
Prior GC-C agonist exposure, n (%)[a]	69 (22.4)	64 (20.9)
Abdominal Score, mean (SD)	6.46 (1.60)	6.39 (1.63)
Abdominal bloating, mean (SD)	6.64 (1.70)	6.56 (1.71)
Abdominal discomfort, mean (SD)	6.47 (1.64)	6.39 (1.64)
Abdominal pain, mean (SD)	6.27 (1.66)	6.22 (1.69)
CSBMs/week, mean (SD)	0.26 (0.53)	0.27 (0.51)
SBMs/week, mean (SD)	1.60 (1.09)	1.72 (1.11)
IBS symptom severity, mean (SD)[b]	3.62 (0.68)	3.59 (0.70)
Constipation severity, mean (SD)[b]	3.72 (0.63)	3.71 (0.73)

[a]Patients who reported prior treatment with linaclotide or plecanatide (both are GC-C agonists approved for the treatment of IBS-C) were allowed to enter the study following a 30-day medication washout.
[b]Assessed on a scale of 1 to 5 (1=none; 5=very severe).
CSBM, complete spontaneous bowel movement; GC-C, guanylate cyclase-C; IBS, irritable bowel syndrome; SBM, spontaneous bowel movement; SD, standard deviation.

Efficacy

- Overall Abdominal Score improvement was significantly greater for patients receiving linaclotide compared to placebo
  - The change from baseline in Abdominal Score for the overall treatment period was –1.898 for linaclotide and –1.182 for placebo (**Figure 2**; **Table 2**)
  - The overall mean percent change from baseline in Abdominal Score was –28.9% for linaclotide vs. –18.8% for placebo
- Abdominal Score improvement was significantly greater for linaclotide vs. placebo patients at each week included in the prespecified fixed-sequence testing analyses (p⩽0.0002)
  - All analyses in the prespecified fixed-sequence testing showed significant treatment benefit for linaclotide vs. placebo patients

Figure 2. LS mean change from baseline in Abdominal Score



*p<0.0001, except for Week 8 (H6) where p=0.0002.
[a]P value based on LS mean changes from baseline. LS means were obtained based on a mixed model with repeated measures analysis with treatment, analysis week, geographic region, and treatment-by-week interactions as fixed effects, and baseline score as a covariate.
LIN, linaclotide; LS, least squares; PBO, placebo; SE, standard error.

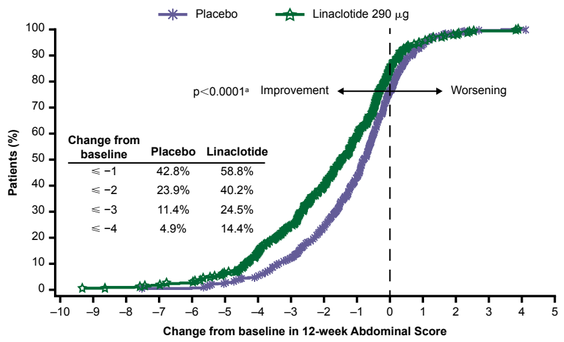
Table 2. Fixed-sequence testing

H.	Fixed sequence for testing	Placebo	Linaclotide	P value
1	CFB in weekly Abdominal Score – overall treatment effect, LS mean (SE)	−1.182 (0.109)	−1.898 (0.111)	<0.0001
2	CFB in 12-week Abdominal Score – cumulative distribution	-	-	-
3	6/12-week Abdominal Score responder, %	23.4	40.5	<0.0001
	CFB in weekly Abdominal Score, LS mean (SE)			
4	At Week 12	−1.480 (0.133)	−2.347 (0.135)	<0.0001
5	At Week 10	−1.478 (0.130)	−2.197 (0.132)	<0.0001
6	At Week 8	−1.446 (0.130)	−2.110 (0.131)	0.0002
7	At Week 6	−1.183 (0.122)	−2.014 (0.124)	<0.0001
8	At Week 4	−1.048 (0.115)	−1.731 (0.117)	<0.0001
9	At Week 2	−0.795 (0.102)	−1.423 (0.104)	<0.0001
10	At Week 1	−0.490 (0.085)	−0.925 (0.087)	<0.0001

Significance was set at p<0.05. Although not all weeks were included in the fixed sequence for testing, CFB in weekly Abdominal Score was greater for linaclotide vs. placebo (p<0.0002) for each week. For weeks not included in the prespecified fixed-sequence testing analysis, Abdominal Score improvement was analyzed outside of the formal testing procedure. For each of these additional weeks, Abdominal Score improvement was greater for linaclotide compared to placebo patients (p<0.0001).
CFB, change from baseline; H, hypothesis number in the fixed sequence; LS, least squares; SE, standard error.

- The 6/12-week Abdominal Score responder rate was 40.5% for linaclotide patients vs. 23.4% for placebo patients (odds ratio=2.2 [95% confidence interval: 1.55, 3.12; p<0.0001])
- Empirical cumulative distribution function curves showed improvement in 12-week Abdominal Score for linaclotide, with significant separation from placebo (p<0.0001; **Figure 3**)

Figure 3. eCDF curves for Abdominal Score



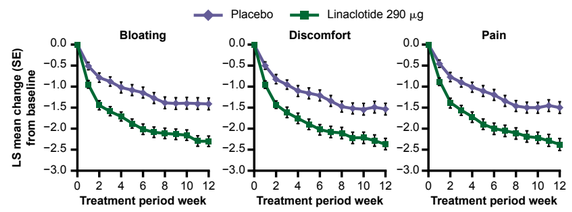
Cumulative distribution function; each plotted point represents a single patient, with the y value for that point representing the cumulative percentage of patients with ⩽ CFB on the x axis.
[a]The p value comparing CFB distributions by treatment was obtained from Wilcoxon rank sum tests. The p value met the criteria for statistical significance under the fixed-sequence testing procedure.
CFB, change from baseline; eCDF, empirical cumulative distribution function.

- Individual abdominal symptoms similarly improved with linaclotide (**Figure 4**)
  - Improvements in individual abdominal symptoms (bloating, discomfort, and pain) appeared similar to the improvements seen in Abdominal Score

Safety

- Diarrhea was the most common treatment-emergent AE (TEAE) [**Table 3**]
  - Most episodes of diarrhea were mild to moderate and no serious AEs of diarrhea were observed
  - Discontinuations due to diarrhea occurred in five patients (1.6%) in the linaclotide group and no patients in the placebo group
  - Exploratory analyses found no correlations between diarrhea TEAEs and prior GC-C exposure
- Symptoms did not worsen relative to baseline in the randomized withdrawal period

Figure 4. Change from baseline in individual abdominal symptoms



LS mean difference (Linaclotide-Placebo)

Overall	−0.747 (p<0.0001)	−0.694 (p<0.0001)	−0.707 (p<0.0001)
Week 1	−0.429 (p=0.0001)	−0.445 (p<0.0001)	−0.431 (p<0.0001)
Week 12	−0.889 (p<0.0001)	−0.837 (p<0.0001)	−0.881 (p<0.0001)

Nominal p=0.0001 for all linaclotide comparisons, except Week 8 for abdominal pain (p=0.0002) and abdominal discomfort (p=0.0005), based on a mixed model with repeated measures analysis with treatment, analysis week, geographic region, and treatment-by-week interactions as fixed effects, and baseline score as a covariate.
LS, least squares; SE, standard error.

Table 3. TEAEs reported in ⩾2% of linaclotide patients during the treatment period (safety population)

AE (preferred term)	Placebo (n=308) n (%)	Linaclotide (n=306) n (%)
Patients with at least 1 TEAE	82 (26.6)	95 (31.0)
Diarrhea	5 (1.6)	14 (4.6)
Headache	3 (1.0)	8 (2.6)
Abdominal pain[a]	7 (2.3)	7 (2.3)
Nausea	5 (1.6)	6 (2.0)
Upper respiratory tract infection	4 (1.3)	6 (2.0)

[a]Abdominal pain includes the preferred terms "abdominal pain," "abdominal pain upper," and "abdominal pain lower."
AE, adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- **Linaclotide significantly improved multiple abdominal symptoms important to patients with IBS-C (abdominal bloating, abdominal discomfort, and abdominal pain) compared with placebo, as measured by the novel, multi-item DIBSS-C Abdominal Score**
- **The safety profile for linaclotide was consistent with previous study results**
- **The Abdominal Score offers a way to measure meaningful improvement in patients treated with linaclotide and can be used in future IBS-C clinical studies to measure clinically meaningful improvements in these three key abdominal symptoms in IBS**

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DISCLOSURES

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