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Linaclotide Reduced Response Time for Irritable Bowel Syndrome With Constipation Symptoms: Analysis of 4 Randomized Controlled Trials

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INTRODUCTION: **These post hoc analyses provide clinically relevant data concerning time to response for individual irritable bowel syndrome with constipation (IBS-C) symptoms after linaclotide use.**

METHODS: **Time-to-response data were pooled from 4 randomized controlled trials. Response time for abdominal symptoms (pain, discomfort, and bloating) and complete spontaneous bowel movements (CSBMs) were analyzed using the Kaplan-Meier method; patients were categorized as early responders (≤4 weeks), late responders (>4–12 weeks), or nonresponders.**

RESULTS: **Among 2,350 patients (1,172 placebo and 1,178 linaclotide 290 μg), >50% of patients with IBS-C who initiated linaclotide treatment experienced a decrease of ≥30% in abdominal pain, discomfort, or bloating within 3–4 weeks (median). The median time to achieving ≥3 CSBMs was 4 weeks. Although not all linaclotide-treated patients responded within 12 weeks, a late response occurred between 4 and 12 weeks in 1 in 6 patients for abdominal pain and in approximately 1 in 10 patients for CSBM frequency. Comparisons of early responders, late responders, and nonresponders for both response definitions indicated that women, Whites, and patients with less severe baseline abdominal symptoms were more likely to respond early.**

DISCUSSION: **Although treatment responses with linaclotide occurred in >50% of patients with IBS-C within 4 weeks of treatment initiation, benefits for individual abdominal symptoms and/or CSBM frequency can still occur between 4 and 12 weeks. A lack of improvement in one symptom does not negate the possibility of response for others, highlighting the importance of discussing all symptoms with patients and not assuming treatment futility at 4 weeks.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C743, http://links.lww.com/AJG/C744

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic condition affecting between 3% and 10% of the global population (1–3). IBS is most common in individuals aged 18–39 years and women (1). The current diagnostic criteria for IBS include recurrent abdominal pain occurring at least 1 day per week, on average, in the past 3 months, associated with 2 or more of the following: pain related to defecation and/or associated with a change in stool form and/or frequency (4,5). Changes in bowel function define the different subtypes of IBS; evidence suggests that patients with IBS with constipation (IBS-C) experience more frequent and bothersome abdominal pain than patients with other subtypes (6).

Owing to its heterogeneous pathogenesis, there is no single effective therapy for IBS, and patients with similar symptoms can respond differently to the same treatment (7). Patients are likely to suffer from chronic symptoms; many patients have complex treatment histories spanning many years and have tried multiple different interventions (8).

Although there are many dietary, behavioral, over-the-counter, or prescription drugs for IBS-C, these have varying degrees of impact on constipation and/or abdominal symptoms

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(7,9–11). Among patients with IBS-C in the United States, less than 15% reported being very satisfied with over-the-counter treatment, and less than 20% had tried a US Food and Drug Administration (FDA)-approved prescription drug. Similarly, physicians reported having low levels of satisfaction with both over-the-counter and prescription drugs for IBS-C (12). Given the variable symptom profile and unpredictable response to treatment, there exists the distinct possibility that a medication that might improve symptoms is discontinued prematurely because of a perceived lack of efficacy. This may mean patients cycle through multiple therapies, leading to exhaustion of available treatments and increased costs. Both clinicians and their patients are, therefore, likely to benefit from more information concerning patterns of time to response for individual IBS symptoms.

These post hoc analyses of pooled data from 4 randomized controlled trials aim to provide such clinically relevant data for the use of linaclotide in patients with IBS-C. Linaclotide is a 14-amino-acid synthetic peptide agonist of guanylate cyclase C approved by the FDA for treating IBS-C at 290 μg (13). Its use for IBS-C is recommended by multiple international societies (10,11,14,15), and the 290 μg once-daily dose ranked first across all end points in a network meta-analysis examining the relative efficacy of all licensed drugs for IBS-C (16). Pivotal phase 3 trials demonstrated that linaclotide improves both abdominal and bowel symptoms significantly in patients with IBS-C (17,18). A trial in patients with IBS-C, using a novel abdominal symptom scoring system derived from the average scores of multiple abdominal symptoms (pain, discomfort, and bloating), demonstrated that linaclotide significantly reduced the composite abdominal score compared with placebo (19).

However, these studies did not analyze the time to onset of response for individual symptoms, nor did they provide data regarding predictors of response. As abdominal symptoms of IBS-C can be separate and distinct from the occurrence of a bowel movement (BM) (20), it is important to understand individual symptom responses. Therefore, in addition to examining time to response for individual abdominal and bowel symptoms, these analyses assessed the temporal relationship between symptom responses in patients treated with linaclotide vs placebo.

METHODS

Study design

For these post hoc analyses, patient data were pooled from 1 phase 2b (NCT02559206) and 3 phase 3 (NCT03573908, NCT00948818, and NCT00938717) randomized controlled trials reported previously (17–19,21). Only data from patients who received the 290 μg immediate-release dose of linaclotide or placebo within the first 12 weeks of the treatment period from each trial were included. All 4 trials were performed at centers across the United States and Canada and were designed, conducted, and reported in compliance with Good Clinical Practice. Institutional review board-approved informed consent was reviewed and signed by all patients before study participation.

Patient population

Eligible patients were adult males and females who met Rome II or Rome III criteria for IBS-C (22,23) and had a baseline abdominal pain severity score of 3 or more, as per FDA guidance. Patients were excluded if they reported loose or watery stools in the absence of laxatives for >25% of BMs in the 12 weeks before screening, had a Bristol Stool Form Scale score of 7 with any spontaneous bowel movement or a score of 6 for >1 spontaneous bowel movement during the 14 days before randomization, or used rescue therapy on the day before or day of randomization.

Assessments

In each of the 4 trials, patients reported daily assessments of abdominal pain, abdominal discomfort, and abdominal bloating (at their worst over the previous 24 hours, each on an 11-point numerical rating scale; 0 = none, 10 = worst possible). Patients also recorded the number of BMs; whether rescue medication was used; and weekly assessments of constipation severity, IBS symptom severity (both using a 5-point ordinal scale; 1 = none, 5 = very severe), and degree of adequate relief of IBS symptoms (yes/no).

Efficacy end points

All trials included in these post hoc analyses assessed change from baseline in abdominal pain, abdominal discomfort, abdominal bloating, and complete spontaneous bowel movements (CSBMs) (17–19,21). In these pooled analyses, response for abdominal pain, abdominal discomfort, and abdominal bloating was defined as an improvement of ≥30% from baseline in the weekly average score for that symptom, as per FDA recommendations. CSBM response was analyzed: an increase of ≥1 CSBMs/week from baseline and achievement of ≥3 CSBMs/week.

To better understand responder characteristics and the temporal relationship between abdominal symptoms and CSBMs, each responder end point was categorized by time: early responders achieved their end point within the first 4 weeks of treatment, late responders achieved their end point after the first 4 weeks, and nonresponders did not reach the predetermined criteria during the 12-week treatment period.

Statistical analysis

Time to response was analyzed for abdominal pain, abdominal discomfort, abdominal bloating, and CSBM frequency using the Kaplan-Meier method. Comparisons with placebo are presented in time-to-response curves for both abdominal symptoms and CSBMs. Because these are post hoc analyses performed on a large sample size, descriptive statistics for baseline characteristics are presented without statistical comparisons among the response group.

RESULTS

Baseline demographics and clinical characteristics

These analyses included 2,350 patients (1,172 placebo and 1,178 linaclotide 290 μg) from the 4 trials. Demographics and baseline characteristics were well balanced across treatment groups, with a mean age of 44.7 and 44.6 years for placebo and linaclotide 290 μg, respectively. Most patients for linaclotide 290 μg were female (87.4%) and White (73.2%) (Table 1).

Time to response: linaclotide vs placebo

Abdominal symptom responses. For linaclotide-treated patients, the median time to response for abdominal pain (Figure 1a) and abdominal discomfort (Figure 1b) was 3 weeks while it was 4 weeks for abdominal bloating (Figure 1c) (vs 6, 7, and 8 weeks, respectively, for placebo). Each time-to-response curve showed a clear and significant separation between linaclotide and placebo ($P < 0.0001$). Although more than 50% of linaclotide-treated patients responded within 4 weeks (early responders), a further

Table 1. Patient clinical characteristics and baseline efficacy variables

Characteristics	Placebo (n = 1,172)[a]	Linaclotide 290 μg (n = 1,178)[a]
Age, yr, mean (range)	44.7 (18–87)	44.6 (19–85)
Female, n (%)	1,017 (86.8)	1,029 (87.4)
Race, n (%)		
Asian	47 (4.0)	56 (4.8)
Black	248 (21.2)	235 (19.9)
White	848 (72.4)	862 (73.2)
Other	29 (2.5)	25 (2.1)
Abdominal pain score, mean (SD)[b]	5.8 (1.74)[c]	5.8 (1.71)
Abdominal discomfort score, mean (SD)[b]	6.2 (1.69)[c]	6.2 (1.65)
Abdominal bloating score, mean (SD)[b]	6.5 (1.83)[c]	6.6 (1.80)
No. of CSBMs/wk, mean (SD)	0.2 (0.49)	0.2 (0.47)

CSBMs, complete spontaneous bowel movements.
[a]Intention-to-treat population, incorporating patients from 4 separate clinical trials.
[b]Scores for individual symptoms were reported on a scale of 0–10, with 0 corresponding to no symptoms and 10 corresponding to the worst possible characterization of that symptom.
[c]Calculated for n = 1,170 patients.

177 (15.0%), 178 (15.1%), and 202 (17.1%) patients were late responders for abdominal pain, abdominal discomfort, or abdominal bloating, respectively.

CSBM frequency response. The median time to experience an increase of ≥1 additional CSBMs/week from baseline was 2 weeks for linaclotide-treated patients vs 4 weeks for placebo (curve separation, $P < 0.0001$; Figure 2a). The median time to achieve ≥3 CSBMs/week was 4 weeks for linaclotide-treated patients; this median time was not reached by placebo-treated patients during the 12-week treatment period (curve separation, $P < 0.0001$; Figure 2b). Overall, 100 patients (8.5%) were late responders to linaclotide using the threshold of an increase of ≥1 additional CSBMs/week from baseline while 128 (10.9%) were late responders using ≥3 CSBMs/week.

Early responders, late responders, and nonresponders: linaclotide-treated patients

Analyses of patient characteristics for early responders, late responders, and nonresponders among linaclotide-treated patients are presented for abdominal pain response and the more stringent threshold of achieving ≥3 CSBMs/week. A contingency table (Figure 3) presenting abdominal pain responders by CSBM responders shows that while 70.5% of linaclotide-treated patients were early responders for one or both parameters, only 37.1% of linaclotide-treated patients were early responders for both parameters; the remaining 33.4% were late responders or nonresponders for one or the other parameter. Importantly, only 18.7% did not meet either response definition by 12 weeks. A contingency table using the less stringent threshold of ≥1 additional CSBMs/week from baseline is shown in Supplementary Figure 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/C743). In this analysis, only 11.9% of linaclotide-treated patients did not meet either response definition by 12 weeks.

Patient characteristics of early responders, late responders, and nonresponders: linaclotide-treated patients

The study population was predominantly female, and of the linaclotide-treated patients, women were more likely to achieve an early response: 58.6% of linaclotide-treated women vs 47.7% of linaclotide-treated men were early abdominal pain responders and 51.9% of linaclotide-treated women vs 40.3% of linaclotide-treated men were early CSBM responders (achieving ≥3 CSBMs/week) (see Supplementary Table 1, Supplementary Digital Content 2, http://links.lww.com/AJG/C744).

For race, although Whites (the largest race group in the study, n = 862) had the highest overall response rate, the Asian and other (non-White patients who did not identify as Black, African American, or Asian) race groups had the highest proportion of late abdominal pain responders. It should be noted that both Asian (n = 56) and other (n = 25) patients were underrepresented in the trials. In all, 25.0% of linaclotide-treated Asian patients and 36.0% of linaclotide-treated patients from the other race group were late abdominal pain responders, vs 13.6% of Black and 14.2% of White linaclotide-treated patients. The Asian group also had the highest proportion of late CSBM responders: 21.4% of linaclotide-treated Asian patients were late responders, vs 12.3% of Black, 9.7% of White, and 12.0% of other linaclotide-treated patients (see Supplementary Table 1, Supplementary Digital Content 2, http://links.lww.com/AJG/C744).

Early abdominal pain responders seemed to have less severe baseline abdominal symptoms and lower anxiety and depression levels in comparison with both late responders and patients who did not reach the response threshold by week 12. Early CSBM responders seemed to have less severe baseline abdominal symptoms and higher CSBM frequency in comparison with late responders and patients who did not reach the response threshold by week 12 (see Supplementary Table 1, Supplementary Digital Content 2, http://links.lww.com/AJG/C744).

DISCUSSION

There are several agents approved for treating the symptoms of IBS-C (7), each with their efficacy and safety established in randomized controlled trials (16). Clinical decisions regarding treatment selection are aided somewhat by the use of FDA-recommended standardized end points across clinical trials, as exemplified by the ability to make indirect comparisons of efficacy between secretagogues in IBS-C (24). Although the dichotomous end point, incorporating responses in both abdominal pain and CSBMs that function together in a single stringent end point (25), is useful for establishing clinical efficacy and in offering a standard of comparison, it does not necessarily provide clinicians with sufficient information to establish treatment plans and set expectations for patients with varying symptom profiles in routine clinical practice.

When treating patients with IBS-C, it is necessary to recognize that multiple symptoms contribute to a patient's experience. The relative burden of each symptom and treatment efficacy will likely vary among individual patients (7,9–11), as will time to response. In clinical practice, providers want to be able to work with their patients to set realistic expectations of symptom improvement and to provide time lines as to when treatment benefits may

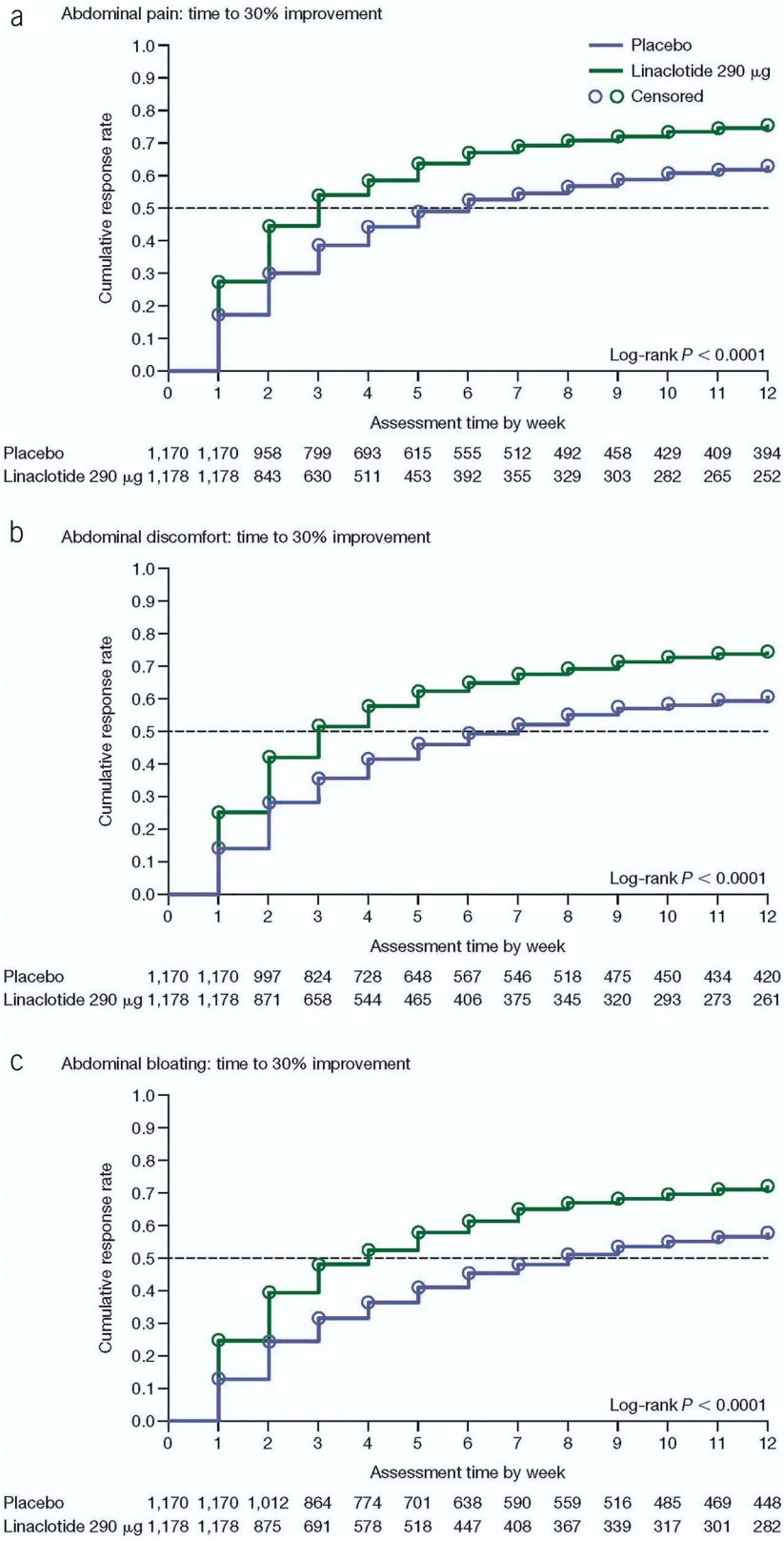

Figure 1. Time-to-response curves for abdominal pain (**a**), abdominal discomfort (**b**), and abdominal bloating (**c**), showing the cumulative proportion of patients per treatment group who are classified as responders as the weeks progress. The number of patients who have not yet met the response definition for each week is presented in the table under each graph. For a patient who does not meet the response criterion before the end of the week 12 cutoff, a censoring flag indicates that (1) the patient had not met the response criterion at a specific visit week and (2) the patient was discontinued from the study. Adapted from ref. 35.

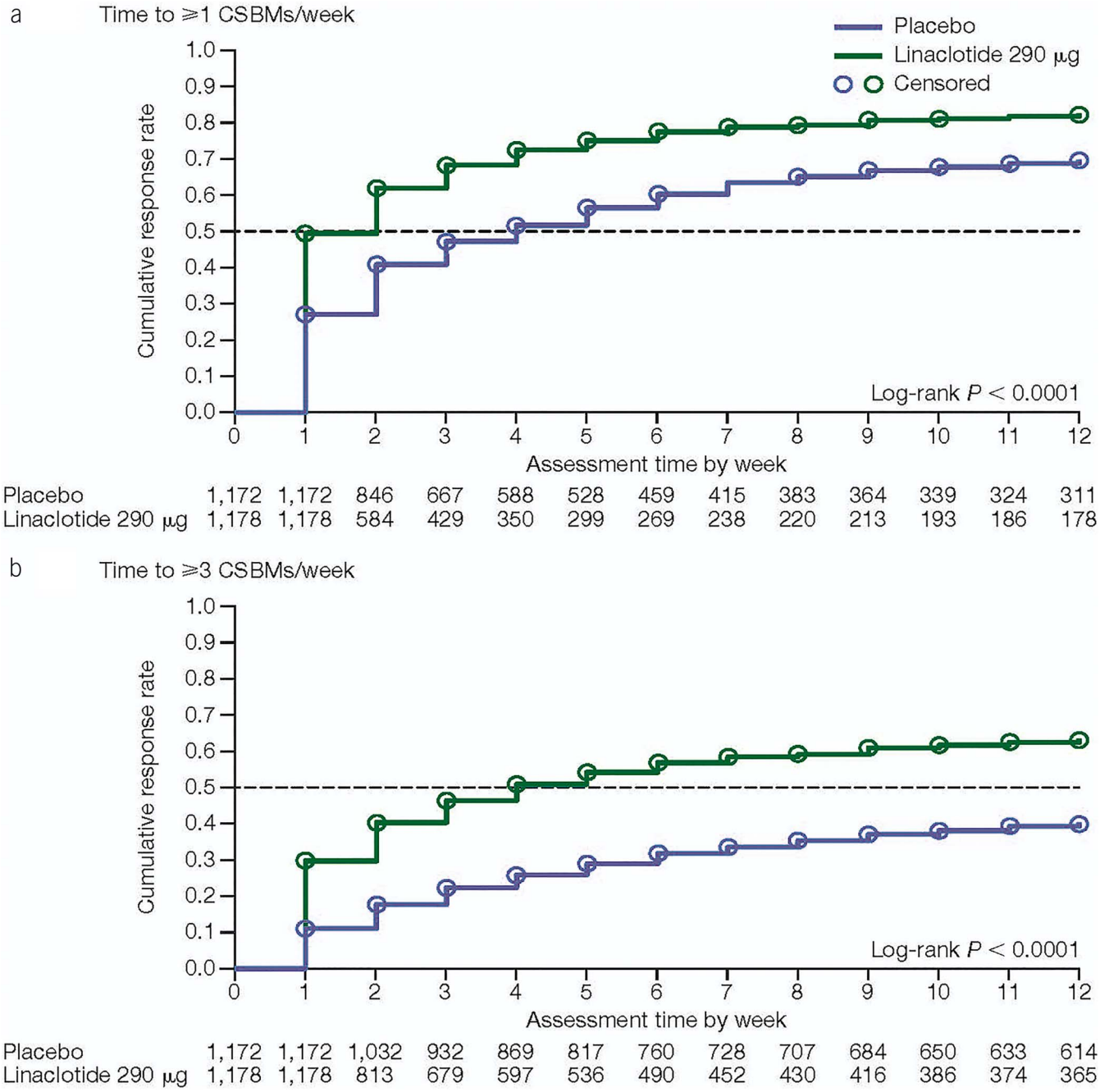

Figure 2. Time-to-response curves for bowel symptoms, showing the cumulative proportion of patients in each treatment group who are classified as responders as the weeks progress. The number of patients who have not yet met the definition of response for each week is presented in the table under each graph. CSBM response was defined as either an increase of ≥1 CSBMs/week from baseline (**a**) or achieving ≥3 CSBMs/week (**b**). A censoring flag indicates that (1) the patient had not met the response criterion at a specific visit week and (2) the patient was discontinued from the study. CSBMs, complete spontaneous bowel movements.

occur. Data concerning these issues will reduce the likelihood of prematurely stopping a treatment, which might benefit the patient subsequently and temper expectations. The analyses presented here provide useful insights into the time to response for individual abdominal symptoms and CSBM frequency and allow examination of patient profiles that may predict time to response. Our analyses suggest that more than half of patients with IBS-C who initiate linaclotide treatment will experience a decrease of ≥30% in the severity of abdominal pain and/or abdominal discomfort within 3 weeks and abdominal bloating within 4 weeks. Of note, the time to CSBM response did not coincide clearly with the time to response for abdominal symptoms. The median time to an increase of ≥1 CSBM from baseline preceded the median time to abdominal symptom responses, but the median time to achieving a normal CSBM frequency (≥3 CSBMs/week) lagged slightly behind both abdominal pain and discomfort responses. This is consistent with known actions of linaclotide in preclinical models (26,27). Further supporting this concept,

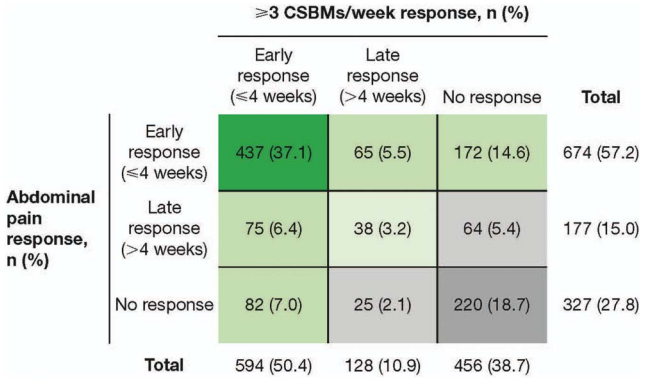

Figure 3. Early responders, late responders, and nonresponders: Abdominal pain responders by those achieving ≥3 CSBMs/week for linaclotide-treated patients (n = 1,178). Early response = response in first 4 weeks; late response = response in weeks 5–12; and no response = no response within the 12-week treatment period. Dark green = early response for both symptoms; light green = early response for one symptom and late/no response for the other; pale green = late response for both symptoms; light gray = late response for one symptom and no response for the other; and dark gray = no response for either symptom. CSBMs, complete spontaneous bowel movements.

studies conducted with delayed release formulations of linaclotide, designed to be released in the distal ileum and colon, suggest that its analgesic and bowel modulatory actions may be mediated by 2 distinct guanylate cyclase C agonism pathways (21).

Our analyses of early and late responders demonstrated variations in patterns of response. Although not all patients within this pooled population responded within 12 weeks, responses occurred later than 4 weeks but before 12 weeks in 1 in 6 patients for abdominal pain and in approximately 1 in 10 patients for CSBM frequency. Importantly, fewer than 1 in 5 patients did not meet criteria for either an abdominal pain or CSBM frequency response by 12 weeks. This emphasizes the need to allow sufficient time for a drug to work. It is of course in the best interests of the patient to suspend treatment in cases of futility or intolerable side effects; however, in certain countries, current guidelines preclude continued treatment with linaclotide in some patients who may still benefit. For example, in the United Kingdom, the National Institute for Health and Care Excellence recommends stopping linaclotide treatment if no response is seen within 4 weeks (28). Our analyses show that before 12 weeks, 1 in 6 and 1 in 10 patients might still have met criteria for an abdominal pain and CSBM frequency response, respectively.

In these analyses, abdominal bloating response lagged behind the response for other abdominal symptoms; reasons for this remain unclear because the pathophysiology of abdominal bloating is not fully understood (29–31). However, it has previously been shown that a BM does not always lead to a reduction in a patient's bloating score (29). Theoretically, medications that accelerate transit, such as linaclotide, should improve abdominal bloating and distension (30). Nonetheless, patients with IBS-C have reported that an improvement in BM frequency is required for them to feel as though an IBS medication is working, although abdominal symptoms are important to patients (32). Different thresholds and symptom-specific changes from baseline should be considered when assessing response (25). From a clinical perspective, it is important for physicians to recognize that an improvement in some symptoms may lag behind others and to challenge how a responder is defined in routine clinical practice, given the variability in response times demonstrated here. Nevertheless, it should be acknowledged that some patients may not be prepared to wait 8–12 weeks for a treatment to work, highlighting the need for an open discussion between patients and healthcare professionals.

Our comparison of early responders, late responders, and nonresponders for both the abdominal pain and CSBM responses showed some differences in demographics and baseline characteristics between the responder groups. The proportions of Asian patients were numerically higher among late responders for both abdominal pain and CSBM frequency. However, it is important to note that Asian patients were under-represented within the trials, so these results will require replication in future studies. In addition, the baseline individual abdominal symptom severity scores (pain, discomfort, and bloating) were higher, on average, among the late responders and those who did not respond within 12 weeks. Furthermore, baseline Hospital Anxiety and Depression Scale-Depression and Hospital Anxiety and Depression Scale-Anxiety scores seemed to be higher in late abdominal pain responders and those who did not respond within 12 weeks.

These results suggest that abdominal symptom severity and psychological health may be associated with a slower time to response. Previous research has found that baseline symptom severity may affect outcomes of treatment with cognitive behavioral therapy for IBS (33). This is supported by another study examining the response time with cognitive behavioral therapy in patients with IBS, in which those who reported adequate relief of pain and bowel symptoms and a ≥50-point decrease in total IBS severity scores by week 4 were classified as rapid responders (34). These rapid responders had more severe IBS symptoms and baseline Irritable Bowel Syndrome Quality of Life Questionnaire scores but did not differ in psychological distress or demographic characteristics compared with other patients (34). Nonetheless, these studies used therapies targeting central mechanisms of pain, whereas linaclotide acts peripherally. Further research is needed in this area.

The strength of these analyses lies within the synthesis of data from multiple studies, resulting in a large sample size. Inevitably, post hoc analyses have limitations associated with multiple testing; in collating data from different trials, there are likely to be differences in patient populations and methods between trials. As with any clinical trial, the study population may not be representative of the real-world disease population because of the stringent definitions of IBS-C used to enroll patients. Within clinical practice, a much greater variation between patients' symptom profiles most likely exists, which may require discussions around individual symptoms and their associated response times to various treatments.

Future trials in IBS would benefit from assessing not only efficacy but also time to response and categorizing early responders, late responders, and nonresponders; however, consensus between responder definitions will need to be reached. Evaluating the different proportions of responders and identifying common characteristics of patients within each category could lead to prospective assessments of predictors of and time to response.

The results of these pooled analyses suggest that although over half of patients with IBS-C treated with linaclotide will experience response for abdominal pain, discomfort, and bloating or CSBM frequency within 4 weeks of treatment initiation, another 8%–17% exhibit a response between weeks 5 and 12. Time to

response differs for individual symptoms, and individual patient characteristics may influence this. A lack of improvement in one symptom does not negate the possibility of a response for others, highlighting how important it is that clinicians review any benefit across all symptoms with patients and do not assume treatment futility at 4 weeks.

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CONFLICTS OF INTEREST

Guarantor of the article: Darren M. Brenner, MD.

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Potential competing interests: D.M.B. has acted as a consultant, advisor, and/or speaker for AbbVie, Adelyx, Alnylam, AlphaSigma, Arena, Laborie, Mahana, QoL Medical, Redhill, Salix, Takeda, and Vibrant Technologies and also serves on the Board of Directors for the International Foundation for GI Disorders (IFFGD). B.E.L. has acted on a scientific advisory board or as a consultant for AbbVie, Allakos, AlphaSigma, Arena, Ironwood, Salix, Takeda, and Vivier. A.C.F. has acted as a consultant and/or speaker for Dr. Falk, GE Healthcare, Ironwood, Novartis, and Takeda Pharmaceuticals. W. Bartolini is a former employee of Ironwood Pharmaceuticals and holds stock and stock options. J.W. is an employee of Ironwood Pharmaceuticals and may hold stock and stock options. E.P.S. and C.A. are former employees of Ironwood Pharmaceuticals. W. Bochenek is a former employee of AbbVie; has been involved in the design, conduct, and assessment of study results of linaclotide studies in IBS-C; and is currently retired. R.B. is an employee of AbbVie and may hold stock and stock options.

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Ethics: All 4 trials were performed at centers across the United States and Canada and were designed, conducted, and reported in compliance with Good Clinical Practice. Institutional Review Board-approved informed consent was reviewed and signed by all patients before study participation.

Data sharing statement: AbbVie and Ironwood are committed to responsible data sharing regarding the clinical trials they sponsor. This includes access to anonymized, individual-level and trial-level data (analysis data sets) and other information (e.g., protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Study Highlights

WHAT IS KNOWN

- ✓ Owing to its heterogeneous pathogenesis, there is no single overall effective therapy for irritable bowel syndrome with constipation (IBS-C).
- ✓ Time to treatment response can be unpredictable for individual patients, potentially leading to the premature discontinuation of a medication that may prove effective.

WHAT IS NEW HERE

- ✓ The time to onset of treatment response with linaclotide for IBS-C varies between individual bowel and abdominal symptoms.
- ✓ A lack of improvement in one IBS-C symptom does not negate the possibility of a treatment response for another.
- ✓ Delayed benefits in abdominal and bowel symptoms, between weeks 5 and 12, occurred in 1 in 6 and approximately 1 in 10 patients, respectively.
- ✓ Premature therapeutic withdrawal may result in unnecessary cycling of therapeutics, exhaustion of available treatment options, and increased health expenditures.

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