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Randomized Trial of 2 Delayed-Release Formulations of Linaclotide in Patients With Irritable Bowel Syndrome With Constipation

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INTRODUCTION: **Immediate-release (IR) formulation of linaclotide 290 μg improves abdominal pain and constipation (APC) in patients with irritable bowel syndrome (IBS) with constipation. Delayed-release (DR) formulations were developed on the premise that targeting the ileum (delayed-release formulation 1 [DR1]) or ileocecal junction and cecum (MD-7246, formerly DR2) would modulate linaclotide's secretory effects while preserving pain relief effects.**

METHODS: **This phase 2b study randomized patients with IBS with constipation to placebo or 1 of 7 once-daily linaclotide doses (DR1 30, 100, or 300 μg; MD-7246 30, 100, or 300 μg; or IR 290 μg) for 12 weeks. Key efficacy endpoints were change from baseline in abdominal pain and complete spontaneous bowel movement frequency, and 6/12-week combined APC+1 responder rate.**

RESULTS: **Overall, 532 patients were randomized; mean age was 45.1 years, and most were women (83.3%) and White (64.7%). All linaclotide DR1 and MD-7246 groups experienced greater improvements in abdominal pain from baseline and vs placebo throughout treatment. Linaclotide DR1 and IR led to numerically greater improvements from baseline in complete spontaneous bowel movement frequency and higher APC+1 responder rates compared with placebo; MD-7246 results were similar to placebo. Diarrhea was the most common adverse event with DR1 and IR; rates were similar between MD-7246 and placebo.**

DISCUSSION: **Altering the site of drug delivery in the intestine might uncouple linaclotide's pain relief from secretory effects. Persistent, modest abdominal pain improvement with limited impact on bowel symptom parameters, as seen across MD-7246 doses, warrants further study of MD-7246 as a novel treatment for abdominal pain, regardless of IBS subtype.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B699, http://links.lww.com/AJG/B700, http://links.lww.com/AJG/B701, and http://links.lww.com/AJG/B702

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain associated with altered bowel habits (1,2). IBS affects approximately 11% of adults globally (3) and significantly reduces quality of life and work productivity (4,5). Although the predominant bowel habit varies from constipation to diarrhea, abdominal pain is the unifying and most bothersome symptom across IBS subtypes (1,6,7). Numerous therapies are used to treat IBS, but few provide relief of both abnormal bowel habits and abdominal pain (8).

Linaclotide is a guanylate cyclase (GC)-C agonist currently approved as an immediate-release (IR) formulation for IBS with constipation (IBS-C) and chronic idiopathic constipation (9). Linaclotide acts locally within the GI tract, enhancing secretion and resulting in increased luminal water content and accelerated bowel transit (10–13). Preclinical evidence suggests that linaclotide inhibits the activity of pain-sensing nerves by increasing extracellular cyclic guanosine monophosphate released through the basolateral membrane of intestinal epithelial cells (14–17). In phase 3 trials, linaclotide IR 290 μg has demonstrated efficacy in

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treating both the constipation and abdominal pain symptoms associated with IBS-C (18,19) with a favorable safety profile (20).

Visceral hypersensitivity is recognized as a central mechanism for abdominal pain in IBS (21). The hypersensitivity typical of IBS is likely complex and might be present throughout the GI tract; however, colonic sensory afferents appear key to the development and persistence of IBS-related abdominal pain (22,23).

Two delayed-release (DR) formulations of linaclotide are under development to target more distal regions of the GI tract, possibly leading to differential effects on abdominal pain and bowel function. Delayed-release formulation (DR) 1 was designed to release linaclotide in the ileum to enhance pain relief and preserve the drug's secretory effects, whereas DR2 (hereafter called MD-7246) was designed to release linaclotide more distally in the ileocecal junction and cecum, to relieve pain originating in the colon and minimize secretory effects in the small bowel (24). The objective of this study was to evaluate the safety, efficacy, and dose response of these 2 DR formulations when administered orally to patients with IBS-C.

METHODS

Study design

A 12-week, randomized, double-blind, double-dummy, placebo-controlled, parallel-group phase 2b clinical trial was conducted at 71 study centers in the United States between October 2015 and September 2016. Patients discontinued prohibited medications for ≥14 days (24 hours for laxatives) during the screening period. Eligible patients entered the pretreatment period and provided daily and weekly symptom assessments with an electronic diary (eDiary). Eligible patients were randomized to placebo or 1 of 7 once-daily linaclotide doses (DR1 30, 100, and 300 μg; MD-7246 30, 100, and 300 μg; or IR 290 μg [positive control]) for 12 weeks. Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B699) reports randomization details. Study visits occurred every 4 weeks (Figure 1).

The trial was designed, conducted, and reported in compliance with ethical principles set forth by the Declaration of Helsinki and Good Clinical Practice guidelines. The research protocol was approved by an institutional review board at each study site, and the trial was registered with ClinicalTrials.gov (NCT02559206).

Patients

Inclusion criteria were as follows: patients aged 18 years or older and who met the Rome III criteria for IBS-C (6); patients who had hard/lumpy stools with ≥25% of bowel movements (BMs) and loose (mushy)/watery stools with <25% of BMs without antidiarrheal medications or laxatives, and experienced <3 BMs per week for the ≥12 weeks during which the IBS-C diagnosis was established; and patients who had average worst abdominal pain ≥3.0 (11-point scale; 0 = none, 10 = worst possible), ≤10 spontaneous BMs (SBMs; BMs occurring without laxative, suppository, or enema use), and ≤6 complete SBMs (CSBMs; SBMs associated with a sensation of complete evacuation) during the 14 days before treatment.

Patients were excluded if they reported loose/watery stools without laxatives for >25% of BMs in the 12 weeks before screening; had a Bristol Stool Form Scale score of 7 with any SBM during the 14 days before randomization; and used rescue therapy on the day before or day of randomization. Other key exclusion criteria were structural alterations or conditions that could impact GI motility and a history of chronic conditions that could be associated with abdominal pain, discomfort, or constipation.

Efficacy assessments and endpoints

Patients recorded the number of BMs and severity of abdominal pain, bloating, and discomfort (11-point scales; 0 = none, 10 = worst possible) daily using eDiary. For each BM, stool consistency (7-point Bristol Stool Form Scale), sensation of complete evacuation (yes/no), and use of rescue therapy were recorded.

Key efficacy endpoints. Key efficacy endpoints were weekly change from baseline (CFB) in abdominal pain (primary endpoint), weekly CFB in CSBM frequency, and a combined abdominal pain and constipation (APC) response. Weekly abdominal pain scores were calculated by averaging daily scores during each week. Weekly CSBM frequency was the total number of CSBMs each week. A patient was an APC+1 responder if they met the following weekly criteria for ≥6 of 12 weeks of treatment: (i) a reduction of ≥30% in the average abdominal pain score compared with the baseline average; and (ii) an increase from baseline of ≥1 in the CSBM weekly rate for that week (18,19). A patient was an APC+1 sustained responder if they met the responder definition and were a weekly responder for ≥2 of the last 4 weeks of treatment.

Additional efficacy endpoints. Additional endpoints included 12-week CFB in abdominal discomfort and bloating, and abdominal pain and adequate relief responder rates. The 12-week CFB values were defined as the average of nonmissing values over the treatment period minus the baseline value. A patient was a 6/12-week abdominal pain responder if they met the weekly abdominal pain responder criteria for ≥6 weeks of the 12-week treatment period; the more stringent 9/12-week abdominal pain responder definition required ≥9 weeks. Table 2 (see Supplementary Digital Content 2, http://links.lww.com/AJG/B700) reports additional endpoints.

Safety assessments

Adverse events (AEs) and serious AEs (SAEs) were documented at each study visit. The investigator at each study site assessed the severity and causal relationship of AEs to study drug. Physical examinations, vital sign measurements, and standard clinical laboratory tests were also performed.

Statistical analysis

The sample size was determined based on the results of the previous linaclotide IR study (18,19), assuming higher doses of each DR formulation would show CFB in abdominal pain similar to historical values for linaclotide IR and lower doses would show CFB approximately 50% of previous treatment differences. Under these assumptions, 65 patients per treatment group (520 total patients) would have 81% power based on a 2-sided linear trend test within each formulation at a type I error of 0.05.

Efficacy analyses were based on an intent-to-treat population (i.e., randomized patients who received ≥1 dose of study drug). No adjustments were made for multiplicity. Nominal *P* values for pairwise comparisons are provided for descriptive purposes only. For key efficacy endpoints, weekly least-squares (LS) mean CFB values are graphed. Overall treatment effects were evaluated using a mixed model repeated measures framework, with fixed effects for the baseline value of the specified measure, week, treatment group, geographic region, and week-by-treatment group. The overall dose response within each DR formulation was assessed with an overall trend test (i.e., linear contrast). Responder rates

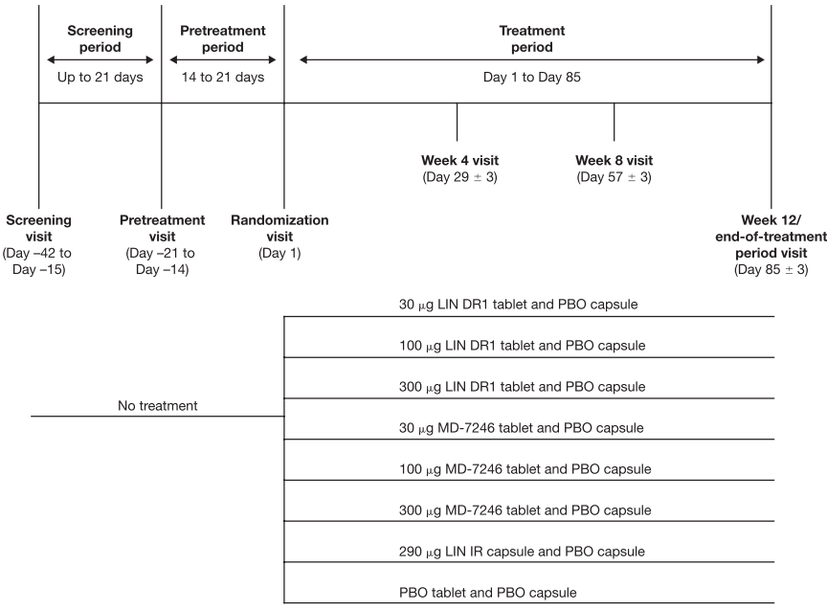

Figure 1. Study design. DR1, delayed-release formulation 1; IR, immediate-release formulation; LIN, linaclotide; PBO, placebo.

were compared between treatment groups using the Cochran-Mantel-Haenszel test, controlling for geographic region; dose response was assessed with Cochran-Mantel-Haenszel correlation statistics. Additional 12-week CFB endpoints were evaluated over the entire treatment period using an analysis of covariance model with fixed effects for treatment group, geographic region, and baseline value of the specific measure. Pairwise comparisons between each linaclotide dose and placebo were performed for all analyses.

RESULTS

Patient disposition, demographics, and baseline characteristics

Of 989 patients screened, 532 were randomized and received ≥1 dose of study drug (intent-to-treat population), and 448 (84.2%) completed the 12-week treatment period (see Figure 1, Supplementary Digital Content 3, http://links.lww.com/AJG/B701). The mean age was 45.1 years, and mean body mass index was 30.0 kg/m^2. Patients were mostly women (83.3%) and White (64.7%). Treatment groups were generally balanced about demographics and baseline clinical characteristics (Table 1).

Key efficacy endpoints

CFB in abdominal pain. All linaclotide DR1 and MD-7246 groups experienced improvements from baseline in abdominal pain throughout the treatment period (Figure 2). Among linaclotide DR1 doses, a dose response was observed for CFB in abdominal pain (trend test, $P < 0.03$), with the 300-μg group showing the greatest improvement over the entire treatment period (LS mean difference from placebo [95% confidence interval (CI)]: −0.771 [−1.419 to −0.123]). The LS mean difference from placebo was −0.569 (95% CI: −1.214 to 0.076) for linaclotide IR and ranged from −0.455 to −0.258 for the 2 lower DR1 doses and all MD-7246 doses, with no dose response seen across MD-7246 doses (trend test, $P = 0.55$).

CFB in CSBM frequency. Over the entire treatment period, the greatest increases in CSBM frequency were seen in the linaclotide IR group (LS mean difference from placebo: 0.992 [95% CI: 0.228–1.756]), followed by the DR1 300-μg group (0.662 [95% CI: −0.104 to 1.428]) (Figure 3). The changes in CSBM frequency seemed to show a dose-response trend across the DR1 doses (trend test, $P = 0.07$). By contrast, CSBM frequencies were similar between the 3 MD-7246 dose groups and placebo over the treatment period, and no dose response was observed (trend test, $P = 0.42$).

APC+1 responder rates. In the linaclotide DR1 dose groups, the percentages of patients who were APC+1 responders were higher than those in the placebo group (odds ratio [OR] [95% CI]: 1.39 [0.61–3.17], 1.27 [0.57–2.85], and 2.39 [1.10–5.19] for DR1 30 μg, 100 μg, and 300 μg, respectively), and a dose response was observed (correlation test, $P < 0.03$) (see Table 2, Supplementary Digital Content 2, http://links.lww.com/AJG/B700). For linaclotide IR, the OR (95% CI) vs of placebo group was 1.71 (0.79–3.70). APC+1 responder rates were similar between the 3 MD-7246 groups and placebo group (ORs ranging from 0.89 to 1.13), with no observed dose response (correlation test, $P = 0.86$). APC+1 sustained responder rates showed similar trends across all doses.

Additional endpoints

The results for additional abdominal and bowel symptom endpoints showed trends across the doses of the 2 formulations that were similar to the trends seen with the primary abdominal and bowel symptom efficacy endpoints (see Table 2, Supplementary Digital Content 2, http://links.lww.com/AJG/B700). Abdominal pain response rates were highest for the linaclotide DR1 300-μg group, followed by the linaclotide DR1 30-μg and MD-7246 300-μg groups. For the most stringent abdominal pain responder threshold (i.e., 9/12-week abdominal pain responder), ORs (95% CIs) vs placebo group were 2.49 (1.14–5.43) for DR1 300 μg, 1.84 (0.83–4.07) for DR1 30 μg, 1.62 (0.75–3.54) for linaclotide IR, and 1.45 (0.65–3.25) for MD-7246 300 μg. For the less stringent threshold (i.e., 6/12-week abdominal pain responder), ORs vs placebo group ranged from 0.85 to 1.11 for all doses, except DR1

Table 1. Summary of patient demographic and baseline clinical characteristics

	PBO (n = 66)	LIN IR 290 μg (n = 66)	LIN DR1 30 μg (n = 67)	LIN DR1 100 μg (n = 67)	LIN DR1 300 μg (n = 67)	MD-7246 30 μg (n = 67)	MD-7246 100 μg (n = 66)	MD-7246 300 μg (n = 66)
Demographics								
Age, yr, mean (SD)	45.4 (14.7)	44.1 (14.4)	44.8 (14.9)	44.7 (13.7)	46.5 (12.7)	42.3 (12.6)	47.9 (12.8)	45.2 (14.4)
BMI, kg/m^2, mean (SD)	30.1 (7.1)	29.7 (5.9)	29.7 (7.9)	29.3 (7.5)	30.4 (7.5)	29.5 (6.9)	29.5 (6.5)	31.5 (7.5)
Women, n (%)	53 (80.3)	53 (80.3)	59 (88.1)	59 (88.1)	55 (82.1)	50 (74.6)	52 (78.8)	62 (93.9)
Race, n (%)								
White	38 (57.6)	43 (65.2)	45 (67.2)	47 (70.1)	41 (61.2)	42 (62.7)	40 (60.6)	48 (72.7)
Other	28 (42.4)	23 (34.8)	22 (32.8)	20 (29.9)	26 (38.8)	25 (37.3)	26 (39.4)	18 (27.3)
Hispanic or Latino	10 (15.2)	14 (21.2)	16 (23.9)	17 (25.4)	16 (23.9)	18 (26.9)	15 (22.7)	21 (31.8)
Clinical characteristics, mean (SD)								
SBMs/wk	1.66 (1.26)	1.78 (1.24)	1.62 (1.16)	1.49 (1.09)	1.73 (1.24)	1.70 (1.04)	1.60 (1.14)	1.65 (1.19)
CSBMs/wk	0.29 (0.56)	0.34 (0.61)	0.35 (0.56)	0.22 (0.46)	0.27 (0.54)	0.35 (0.62)	0.31 (0.61)	0.33 (0.56)
Stool consistency (BSFS)[a]	2.25 (1.13)	2.21 (0.99)	2.35 (1.13)	2.28 (0.90)	2.17 (1.06)	2.30 (1.01)	2.35 (0.90)	2.18 (0.93)
Abdominal pain	6.41 (1.85)	6.18 (1.77)	6.20 (1.59)	6.18 (1.67)	6.38 (1.82)	6.07 (1.68)	6.48 (1.53)	6.09 (1.68)
Abdominal discomfort	6.58 (1.72)	6.29 (1.67)	6.45 (1.38)	6.34 (1.64)	6.70 (1.68)	6.35 (1.61)	6.67 (1.51)	6.36 (1.61)
Abdominal bloating	6.67 (2.16)	6.40 (1.91)	6.67 (1.41)	6.52 (1.74)	6.99 (1.55)	6.52 (1.62)	6.91 (1.57)	6.56 (1.66)

BMI, body mass index; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; DR1, delayed-release formulation 1; IR, immediate-release formulation; LIN, linaclotide; PBO, placebo; SBM, spontaneous bowel movement.
[a]Sample sizes for stool consistency were as follows: n = 59 (placebo), n = 62 (LIN IR 290 μg), n = 62 (LIN DR1 30 μg), n = 56 (LIN DR1 100 μg), n = 61 (LIN DR1 300 μg), n = 61 (MD-7246 30 μg), n = 58 (MD-7246 100 μg), and n = 55 (MD-7246 300 μg).

300 μg (OR [95% CI]: 2.03 [0.99–4.16]) and DR1 30 μg (OR [95% CI]: 1.44 [0.70–2.98]).

Safety

No patients from the linaclotide DR1 or MD-7246 groups experienced SAEs, and no deaths occurred during the study. Treatment-emergent AEs (TEAEs) experienced by ≥2% of patients during the treatment period are reported in Table 3 (see Supplementary Digital Content 4, http://links.lww.com/AJG/B702). In general, the frequency of TEAEs was similar between the linaclotide DR1 and IR groups, and the frequency of TEAEs for the MD-7246 group was similar to the placebo group.

Diarrhea was the most common TEAE in the linaclotide DR1 and IR groups (Figure 4). Diarrhea was reported by 2 (3.0%), 5 (7.5%), and 7 (10.4%) patients in the linaclotide DR1 30-μg, 100-μg, and 300-μg groups, respectively, and 9 patients (13.6%) in the IR group. The frequency of diarrhea was generally lower in the MD-7246 and placebo groups, having been reported by none, 1 (1.5%), and 2 (3.0%) patients in the MD-7246 30-μg, 100-μg, and 300-μg groups, respectively, and 1 patient (1.5%) in the placebo group. Two patients each (3.0%) in the DR1 100-μg and 300-μg groups and 4 patients (6.1%) in the IR group discontinued the study drug due to diarrhea (Figure 4). Two other TEAEs led to study drug discontinuation in the DR1 and MD-7246 groups: headache (DR1 30 μg [n = 1] and DR1 100 μg [n = 1]) and nausea (DR1 100 μg [n = 1] and MD-7246 100 μg [n = 1]). Additional TEAEs leading to discontinuation in the IR group included abdominal pain, defecation urgency, and rectal hemorrhage (for each, n = 1).

One patient in the placebo group experienced SAEs of pneumonia and sepsis, and 1 patient in the linaclotide IR group experienced gastroenteritis. These SAEs were considered unrelated to the study drug by the study investigator, and all SAEs resolved without study drug discontinuation. There were no clinically meaningful differences between treatment groups in the incidence of abnormal vital signs or laboratory parameters.

DISCUSSION

Physicians and patients alike recognize the need for effective therapies to manage the APC symptoms of IBS-C. The 2018 American College of Gastroenterology Monograph on the management of IBS recognized only 3 evidence-based treatment options for patients with IBS-C (8). However, no available pharmacotherapies for IBS are recognized as pure "visceral analgesics," having isolated benefit for abdominal pain without a discernable impact on bowel habits.

Linaclotide's analgesic and secretory effects and its modulation of bowel function might be mediated by 2 distinct pathways, each initiated by GC-C agonism within the GI tract. Distinct pathways would suggest the possibility of reformulating linaclotide to uncouple the pain benefit from its bowel effects. Net flux of water into the luminal bowel, in response to linaclotide's activation of GC-C, is greatest in the more proximal portions of the small bowel (e.g., duodenum and jejunum) (13). Two DR formulations of linaclotide, DR1 and MD-7246, were developed with the intention of exploring the possibility of differential effects of linaclotide on secretion and pain modulation based on delivery to more distal segments of the bowel. It was hypothesized that by bypassing GC-C receptors in the

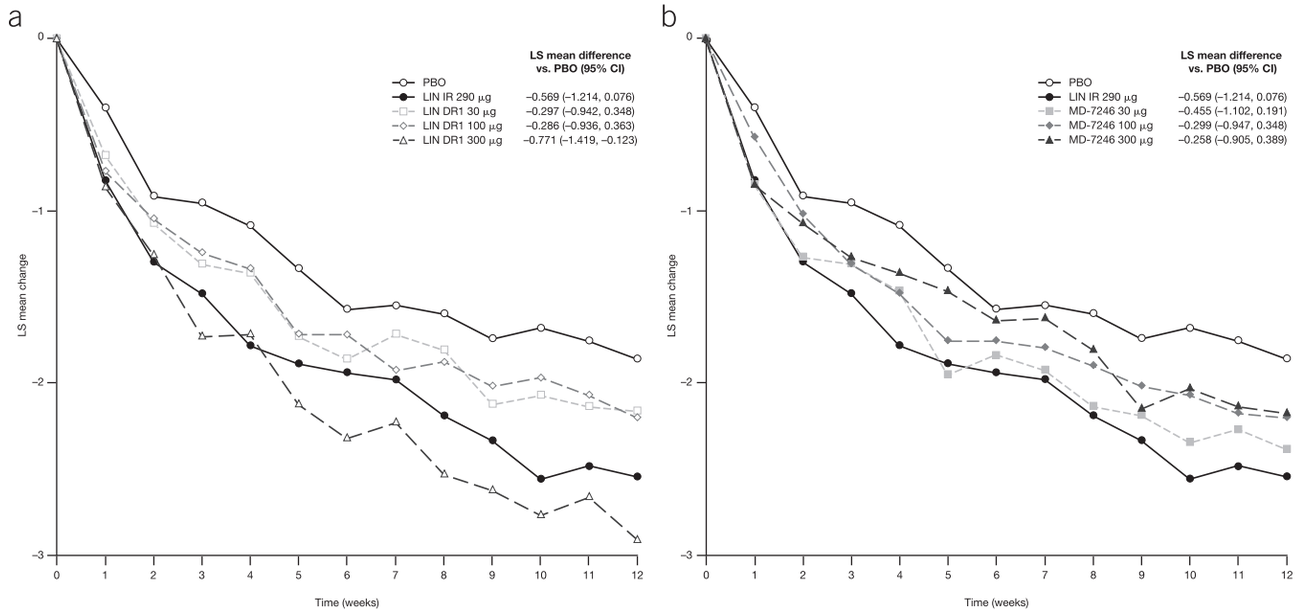

Figure 2. Weekly CFB in abdominal pain. Treatment effects of (**a**) LIN DR1 30 μg, 100 μg, and 300 μg and (**b**) MD-7246 30 μg, 100 μg, and 300 μg are shown with respect to LIN 290 μg IR and PBO, with 12-week LS mean differences vs PBO reported in each legend. All 8 treatment groups were evaluated in a single model, wherein treatment group was included as a fixed effect. CFB, change from baseline; CI, confidence interval; DR1, delayed-release formulation 1; IR, immediate-release formulation; LIN, linaclotide; LS, least-squares; PBO, placebo.

proximal small bowel, these novel DR formulations of linaclotide might have less fluid secretion and, thus, a limited or no effect on bowel habits. At the same time, these DR preparations were expected to retain antinociceptive effects through modulation of sensory afferent pain signaling originating in the colon.

Indeed, this hypothesis seems to have been confirmed in this phase 2b trial in patients with IBS-C. DR1, targeting the ileum, demonstrated similar results at the 300-μg dose when compared with the linaclotide IR formulation for each of the 3 key efficacy endpoints (i.e., weekly CFB in abdominal pain and CSBM

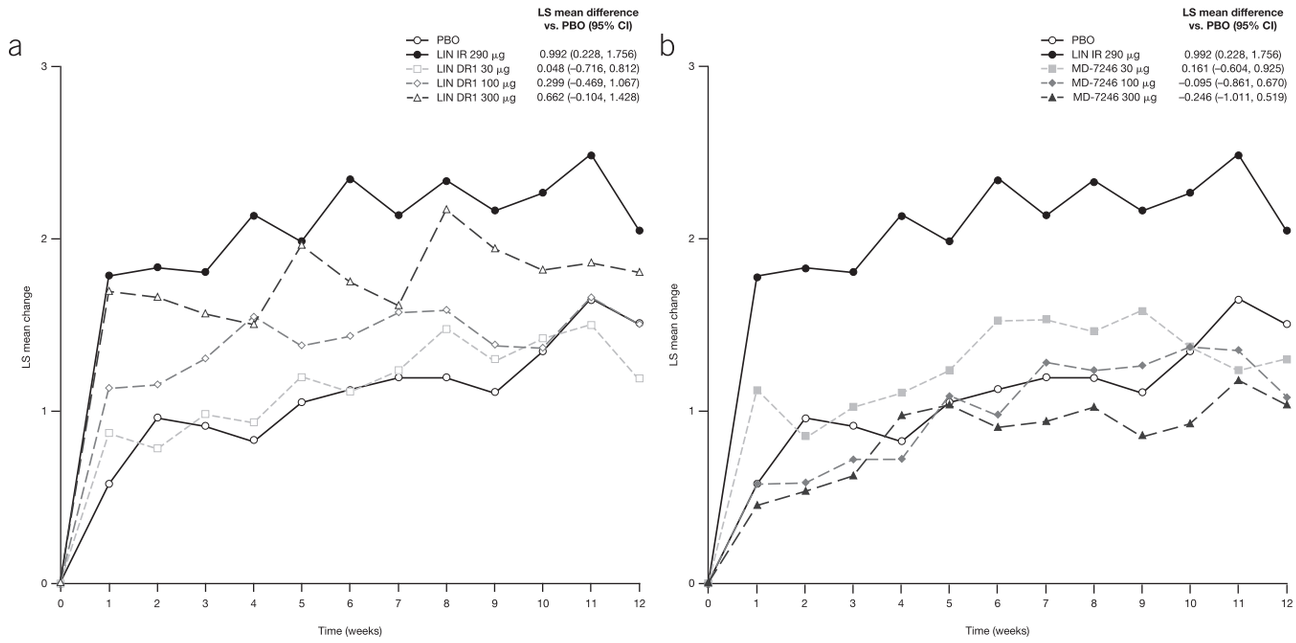

Figure 3. Weekly CFB in CSBM frequency. Treatment effects of (**a**) LIN DR1 30 μg, 100 μg, and 300 μg and (**b**) MD-7246 30 μg, 100 μg, and 300 μg are shown with respect to LIN 290 μg IR and PBO, with 12-week LS mean differences vs PBO reported in each legend. All 8 treatment groups were evaluated in a single model, wherein treatment group was included as a fixed effect. CFB, change from baseline; CI, confidence interval; CSBM, complete spontaneous bowel movement; DR1, delayed-release formulation 1; IR, immediate-release formulation; LIN, linaclotide; LS, least-squares; PBO, placebo.

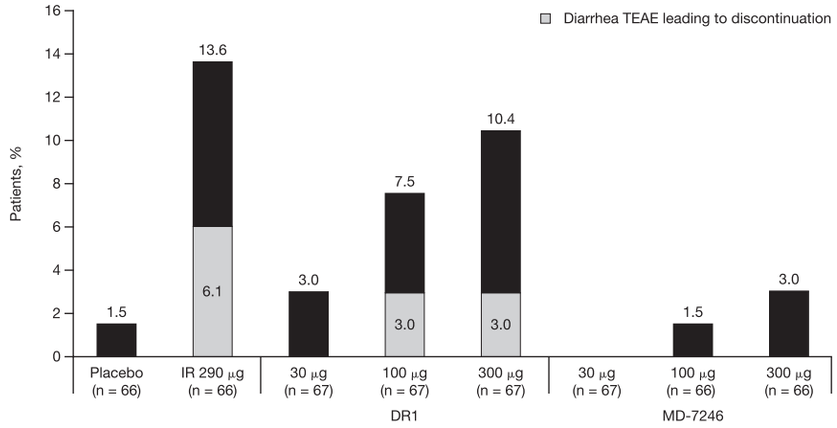

Figure 4. Percentage of patients with diarrhea TEAEs, including those leading to discontinuation. The proportion of patients with diarrhea TEAEs leading to discontinuation (grey) is shown as a subset of the total population with ≥1 diarrhea TEAE in each treatment group. DR1, delayed-release formulation 1; IR, immediate-release formulation; TEAE, treatment-emergent adverse event.

frequency, and APC+1 responder rate). Furthermore, linaclotide DR1 led to greater improvements compared with placebo for the additional endpoints of abdominal bloating, abdominal discomfort, abdominal pain responder rate, and adequate relief responder rate. MD-7246 demonstrated a signal for relief of abdominal pain compared with placebo, with absolute reductions in abdominal pain from baseline (a key endpoint) in all 3 dose groups over the treatment period. The anatomic origin of abdominal pain in IBS remains uncertain. Several studies have clearly demonstrated greater rectosigmoid sensitivity in patients with IBS compared with healthy volunteers using barostat or balloon distention protocols (25,26). Yet, considerable variation in perception can be discerned among patients with IBS-C (27). Furthermore, detectable hypersensitivity of the rectosigmoid might be modulated by physiologic activities in the small intestine, such as the consumption of a meal (28). The similar levels of pain relief observed in this study with IR 290 μg, DR1 300 μg, and MD-7246 suggest that GC-C activation and subsequent release of extracellular cyclic guanosine monophosphate into the distal small bowel and colon might be sufficient to elicit the desired nociceptive effects of GC-C agonism. Trends seen for MD-7246 vs placebo for the key abdominal endpoint, plus those seen for the additional abdominal endpoints, support the antinociceptive properties expected for this formulation and suggest that a portion of linaclotide's analgesic properties might also be mediated by GC-C action in the more proximal small intestine. At the same time, MD-7246 exerted little effect on BM frequency, with no dose response for CSBM frequency or APC+1 responder rates. Data from this study, with sample sizes appropriate for phase 2b exploration, suggest that linaclotide's treatment effects could indeed be modulated by targeting drug delivery to specific parts of the GI tract. With its pharmacologic effects limited to visceral analgesia, MD-7246 presents an intriguing option for the management of nonconstipated subtypes of IBS.

Both the linaclotide DR1 and MD-7246 formulations were well tolerated. The TEAE profile for linaclotide DR1 was consistent with the established safety profile for linaclotide IR 290 μg (18–20), with diarrhea being the most common AE. TEAEs, including diarrhea, were similar between the MD-7246 and placebo groups and were relatively lower than those in the linaclotide DR1 and IR groups. The diarrhea rate in the IR 290-μg group was lower than that seen in the pivotal phase 3 trials (19.5%–19.7% vs 2.5%–3.5% for placebo) (18,19). The reason for this is unknown, although a possible explanation is that, unlike the previous studies, this study did not include a 2-week study visit. No SAEs were reported in patients receiving linaclotide DR1 or MD-7246.

This study has several notable strengths, including the enrollment of a carefully phenotyped patient population who met the Rome III criteria for IBS-C. Patients with potentially important clinical confounders (e.g., structural disease) were excluded. Endpoints examined in this study, including abdominal pain using an 11-point numerical rating scale, followed US Food and Drug Administration guidance for clinical trials in IBS (29). However, this study also has limitations. Although drug delivery to specified bowel segments was expected based on the *in vitro* release profiles of the DR formulations in biorelevant dissolution media, verification of drug delivery using sampling or imaging techniques was not performed *in vivo*. It is conceivable that the precise location of linaclotide delivery with the DR formulations might have varied based on the intestinal bacterial and biochemical milieu of individual patients and/or with different rates of intestinal transit. In addition, results for this study must be considered relative to the limited sample size (66–67 patients per treatment arm) and limited inferential statistical analyses, which focused on the primary endpoint and evaluation of dose trends.

In conclusion, in this phase 2b study of 2 novel linaclotide DR formulations, DR1 seemed to have similar efficacy for improvements in bowel function and abdominal pain compared with the commercially available IR preparation. Importantly, MD-7246 maintained improvement in abdominal pain relief relative to placebo with little impact on bowel symptoms and very low rates of treatment-associated diarrhea. MD-7246 should, therefore, be examined as an option for treating IBS-related abdominal pain without altering bowel habits. Further MD-7246 studies across the spectrum of IBS subtypes, including those with diarrhea predominance, should be considered based on these observations.

CONFLICTS OF INTEREST

Guarantor of the article: Wilmin Bartolini, PhD.

Specific author contributions: W.B., D.S.R., S.M.F., W.B., and K.T. contributed to the conception and design of the study. D.S.R. and K.T. contributed to the analysis of the data. All authors contributed to

Study Highlights

WHAT IS KNOWN

- ✓ Linaclotide IR (Linzess®) is a 14-amino-acid peptide, structurally related to 2 gut hormones (guanylin/uroguanylin).
- ✓ Linaclotide IR exerts prosecretory effects in the small intestine.
- ✓ Linaclotide IR improves APC symptoms associated with IBS-C.
- ✓ Optimal bowel target areas for linaclotide delivery to maximize pain relief remain unclear.

WHAT IS NEW HERE

- ✓ Linaclotide DR1, targeting the ileum, improved APC, similar to IR.
- ✓ MD-7246, targeting the more distal ileocecal junction/cecum, showed modest pain improvement without affecting bowel symptoms.
- ✓ Drug delivery to distal small bowel might modulate linaclotide's secretory effects while preserving analgesic effects.
- ✓ GC-C–activated secretory effects are minimized by limited exposure to the ileum and colon.
- ✓ GC-C activation throughout the GI tract seems to lead to antinociceptive effects.

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