ORIGINAL ARTICLE

Two Randomized Trials of Linaclotide for Chronic Constipation

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ABSTRACT

BACKGROUND

Linaclotide is a minimally absorbed peptide agonist of the guanylate cyclase C receptor. In two trials, we aimed to determine the efficacy and safety of linaclotide in patients with chronic constipation.

METHODS

We conducted two randomized, 12-week, multicenter, double-blind, parallel-group, placebo-controlled, dual-dose trials (Trials 303 and 01) involving 1276 patients with chronic constipation. Patients received either placebo or linaclotide, 145 μg or 290 μg, once daily for 12 weeks. The primary efficacy end point was three or more complete spontaneous bowel movements (CSBMs) per week and an increase of one or more CSBMs from baseline during at least 9 of the 12 weeks. Adverse events were also monitored.

RESULTS

For Trials 303 and 01, respectively, the primary end point was reached by 21.2% and 16.0% of the patients who received 145 μg of linaclotide and by 19.4% and 21.3% of the patients who received 290 μg of linaclotide, as compared with 3.3% and 6.0% of those who received placebo (P<0.01 for all comparisons of linaclotide with placebo). Improvements in all secondary end points were significantly greater in both linaclotide groups than in the placebo groups. The incidence of adverse events was similar among all study groups, with the exception of diarrhea, which led to discontinuation of treatment in 4.2% of patients in both linaclotide groups.

CONCLUSIONS

In these two 12-week trials, linaclotide significantly reduced bowel and abdominal symptoms in patients with chronic constipation. Additional studies are needed to evaluate the potential long-term risks and benefits of linaclotide in chronic constipation. (Funded by Ironwood Pharmaceuticals and Forest Research Institute; ClinicalTrials.gov numbers, NCT00765882 and NCT00730015.)

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Chronic constipation affects between 12 and 19% of the U.S. population.[1,2] The symptoms of chronic constipation, including infrequent bowel movements, hard stools, straining during defecation, bloating, abdominal discomfort, and a sense of incomplete evacuation,[3] adversely affect quality of life[4,5] and are associated with substantial costs.[6,7] Few currently available therapies for chronic constipation have been shown to be effective and safe in well-controlled, long-term trials,[8] and many persons with this disorder are not completely satisfied with their current treatment options.[4]

Linaclotide is a 14-amino-acid synthetic peptide that is structurally related to the endogenous guanylin peptide family. It binds to and activates the guanylate cyclase C receptor on the luminal surface of the intestinal epithelium. Activation of guanylate cyclase C results in the generation of cyclic guanosine monophosphate (cGMP), the levels of which increase both extracellularly and intracellularly. Within the intestinal epithelial cells, the increase in cGMP triggers a signal-transduction cascade that activates the cystic fibrosis transmembrane conductance regulator.[9-11] This activation causes secretion of chloride and bicarbonate into the intestinal lumen, increasing luminal fluid secretion and accelerating intestinal transit.[12] In animal models, linaclotide has been shown to increase gastrointestinal transit and to reduce visceral pain.[13,14]

The objective of these two phase 3 trials (Trial 303 and Trial 01) was to assess the efficacy and safety of once-daily administration of 145-μg and 290-μg doses of linaclotide for 12 weeks to patients with chronic constipation.

METHODS

STUDY DESIGN

We conducted two randomized, 12-week, multicenter, double-blind, parallel-group, placebo-controlled, dual-dose trials at 204 clinical centers in the United States and at 8 clinical centers in Canada from August 20, 2008, through August 12, 2009. The trials were identical except that Trial 303 included a 4-week period of randomized withdrawal at the conclusion of the 12-week treatment period. Patients were randomly assigned in equal proportions to one of three groups. Randomization was performed centrally by means of a computer-generated schedule in blocks of 6 and was balanced within each site. Patients, trial-center personnel, and sponsor staff were not aware of the group assignments.

These trials were designed, conducted, and reported in accordance with the principles of the Good Clinical Practice guidelines. Before participating in the trial, patients at each center reviewed and signed an informed-consent document that had been approved by the institutional review board. The trials were conducted in accordance with the protocols, which are available with the full text of this article at NEJM.org.

During an initial screening period of up to 21 days, patients in both trials provided blood and urine samples for routine testing and were asked to discontinue any prohibited medications (e.g., anticholinergic agents, narcotics, and laxatives) at least 14 days (24 hours for laxatives) before the baseline period. Patients who met the inclusion criteria then entered a 14-day baseline period and used an interactive voice-response system to provide daily and weekly assessments of symptoms. Patients eligible for the 12-week treatment period were randomly assigned (in a ratio of 1:1:1) to receive 145 μg or 290 μg of linaclotide or placebo, in the form of an oral capsule administered once daily at least 30 minutes before breakfast. These dose-strength designations reflect specific linaclotide content rather than total peptide content, as specified in the trial protocols, since linaclotide content is a more accurate and precise indication of dose strength. The actual amount of linaclotide received by patients did not change throughout the two trials.

After completing the treatment period, patients in Trial 303 entered a 4-week, double-blind period of randomized withdrawal to a once-daily study regimen as follows: patients who had received linaclotide during the preceding 12-week treatment period were randomly assigned (in a ratio of 1:1) to either the linaclotide dose they had been assigned initially or placebo, and patients who had received placebo during the treatment period were assigned to 290 μg of linaclotide. Patients made daily calls to the interactive voice-response system throughout the baseline and treatment periods and the period of randomized withdrawal.

In addition to a screening visit, return visits for both trials took place at the start of the baseline period (on day −14), throughout the treatment period (on days 1, 15, 29, 57, and 85),

Table 1. Demographic and Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Trial 303				Trial 01			
	Placebo (N=209)	Linaclotide		P Value†	Placebo (N=215)	Linaclotide		P Value†
		145-μg Dose (N=217)	*290-μg Dose (N=216)*			*145-μg Dose (N=213)*	*290-μg Dose (N=202)*	
Mean age (range) — yr	49 (18–85)	47 (19–82)	48 (18–83)	0.26	47 (20–76)	49 (20–83)	47 (20–82)	0.53
Age ≥65 yr — no. of patients (%)	28 (13.4)	27 (12.4)	27 (12.5)	0.97	27 (12.6)	24 (11.3)	21 (10.4)	0.77
Sex — no. of patients (%)				0.94				0.48
Female	182 (87.1)	191 (88.0)	188 (87.0)		196 (91.2)	195 (91.5)	179 (88.6)	
Male	27 (12.9)	26 (12.0)	28 (13.0)		19 (8.8)	18 (8.5)	23 (11.4)	
Race — no. of patients (%)‡				0.68				0.88
Black	46 (22.0)	46 (21.2)	52 (24.1)		42 (19.5)	41 (19.2)	46 (22.8)	
White	160 (76.6)	164 (75.6)	157 (72.7)		168 (78.1)	168 (78.9)	152 (75.2)	
Body-mass index§	28±5.4	28±6.5	28±5.3	0.96	29±7.2	28±5.2	28±5.8	0.07
CSBMs — no./wk	0.3±0.6	0.3±0.6	0.2±0.4	0.12	0.3±0.5	0.3±0.5	0.3±0.6	0.95
SBMs — no./wk	2.0±1.6	2.1±1.6	2.0±1.6	0.77	1.8±1.4	1.9±1.5	1.9±1.6	0.58
Stool-consistency score¶	2.4±1.0	2.4±1.0	2.5±1.1	0.42	2.3±1.0	2.4±1.1	2.3±1.1	1.00
Straining score‖	3.2±0.9	3.1±0.8	3.3±0.9	0.20	3.2±0.8	3.2±0.9	3.3±0.8	0.49
Abdominal-discomfort score**	2.5±0.8	2.5±0.8	2.5±0.8	0.78	2.6±0.8	2.5±0.9	2.5±0.9	0.57
Bloating score**	2.7±0.9	2.8±0.9	2.8±0.9	0.77	2.8±0.9	2.8±0.8	2.7±1.0	0.72
Constipation-severity score**	3.3±0.7	3.2±0.8	3.3±0.7	0.52	3.3±0.7	3.3±0.7	3.3±0.7	0.61

* Plus–minus values are means ±SD. CSBM denotes complete spontaneous bowel movement, and SBM spontaneous bowel movement.
† P values were calculated with the use of analysis of variance for continuous data and the Cochran–Mantel–Haenszel test for categorical data.
‡ Race was self-reported.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Stool consistency was assessed with the use of the 7-point Bristol Stool Form Scale, where 1 indicates separate, hard lumps, like nuts (hard to pass); 2 sausage-shaped but lumpy; 3 like a sausage but with cracks on the surface; 4 like a sausage or snake, smooth and soft; 5 soft blobs with clear-cut edges (passed easily); 6 fluffy pieces with ragged edges or a mushy stool; and 7 watery, no solid pieces (entirely liquid).
‖ Straining was assessed by means of a 5-point ordinal scale with the following responses, where 1 indicates not at all, 2 a little bit, 3 a moderate amount, 4 a great deal, and 5 an extreme amount.
** Abdominal discomfort, bloating, and constipation severity were all assessed with the use of a 5-point ordinal scale: 1 indicates none, 2 mild, 3 moderate, 4 severe, and 5 very severe.

and, in the case of Trial 303, on days 15 and 29 of the randomized withdrawal period. All personnel involved in the design and implementation of each trial remained unaware of the treatment assignments until the database was locked.

The trials were designed by Ironwood Pharmaceuticals, Forest Laboratories, and the first author. Data collection was monitored by ICON Clinical Research, under the supervision of Ironwood Pharmaceuticals, and by Forest Laboratories, and the data were analyzed by personnel at Ironwood Pharmaceuticals and Forest Laboratories. All the authors vouch for the completeness and veracity of the data and the analyses. The initial draft of the manuscript was written by the first author, and all the authors reviewed the initial draft and contributed to the revision of the manuscript. The decision to submit the article for publication was made by all the authors.

ELIGIBILITY CRITERIA

Men and women 18 years of age or older were eligible if they met the following criteria for chronic constipation: they reported having had fewer than three spontaneous bowel movements (SBMs) per week (occurring without the use of a laxative, enema, or suppository within the preceding 24 hours) and having had one or more of the following signs or symptoms during more than 25% of bowel movements for at least 12 weeks (not necessarily consecutive) within the preceding 12 months: straining, lumpy or hard stools, and a

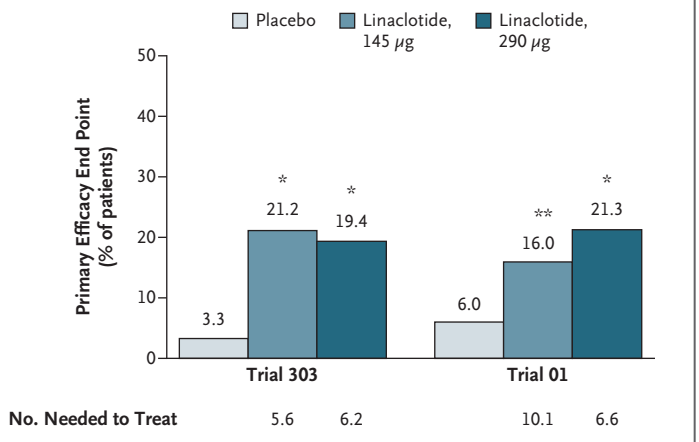

Figure 1. Primary Efficacy End Point in the Linaclotide and Placebo Groups in Each Trial.

The primary efficacy end point was defined as a weekly frequency of three or more complete spontaneous bowel movements (CSBMs) and an increase of one or more CSBMs from baseline for at least 9 weeks of the 12-week treatment period. *P≤0.001, vs. placebo; **P≤0.01, vs. placebo.

sensation of incomplete evacuation. In addition, patients needed to report an average of six or fewer SBMs per week and fewer than three complete SBMs (CSBMs) per week (defined as those for which the patient reported a feeling of complete evacuation) during the 14-day baseline period.

Key exclusion criteria were a report of loose (mushy) or watery stool in the absence of laxative use for more than 25% of bowel movements during the 12 weeks preceding the trials; mushy stool (defined as a score of 6 on the Bristol Stool Form Scale [BSFS],[15] which ranges from 1 to 7, with higher scores indicating more liquid stool and lower scores indicating harder stool) for more than one SBM or watery, liquid stool (a BSFS score of 7) for any SBM during the baseline period; Rome II criteria for the irritable bowel syndrome; and a history of pelvic-floor dysfunction. Colonoscopy was required for patients 50 years of age or older and for patients of any age with unexplained and clinically significant "alarm" symptoms (e.g., lower gastrointestinal bleeding, iron-deficiency anemia, clinically significant unexplained weight loss, systemic signs of infection, or colitis).[16] Patients were asked to refrain from making any major lifestyle changes (e.g., starting a new diet or changing their exercise pattern) during the trial.

STUDY END POINTS

The primary end point of the trials was defined as both three or more CSBMs per week and an increase of at least one CSBM per week from baseline for 9 or more weeks during the 12-week treatment period. Secondary end points included stool frequency (weekly rates of CSBMs and SBMs), stool consistency, severity of straining, abdominal discomfort, bloating, and constipation severity during the 12 weeks of the study. A number of additional end points were assessed, including constipation relief, satisfaction with treatment, the likelihood of treatment continuation, and health-related quality of life.

ASSESSMENTS

The following assessments by patients were recorded daily by means of the interactive voice-response system: the number of bowel movements and whether rescue medication was used; a sensation of complete bowel emptying (yes or no); stool consistency (scored with the use of the 7-point BSFS); and degree of straining, severity of abdominal discomfort, and severity of bloating (all scored on a 5-point ordinal scale, with higher scores indicating more severe symptoms). Constipation severity (based on a 5-point ordinal scale, with higher scores indicating greater severity) and constipation relief (based on a 7-point balanced scale, with 1 indicating complete relief, 4 indicating no change, and 7 indicating very severe constipation) were recorded weekly.

Satisfaction with the trial medication's ability to relieve constipation symptoms (treatment satisfaction) was assessed with the use of a 5-point ordinal scale at all visits during both the treatment period and the randomized withdrawal period. The likelihood that patients would continue taking the trial medication (treatment continuation) was assessed with the use of a 5-point ordinal scale (with higher scores indicating greater satisfaction) at the end of the treatment period and, for Trial 303 only, at the end of the randomized withdrawal period. Health-related quality of life was assessed with the use of the validated Patient Assessment of Constipation Quality of Life (PAC-QOL) instrument[17] at baseline, at week 12, and, for Trial 303 only, at the end of the randomized withdrawal period. Each item was scored from 0 to 4, with lower score indicating better quality of life. The site investigators assessed all patient-reported adverse events and serious ad-

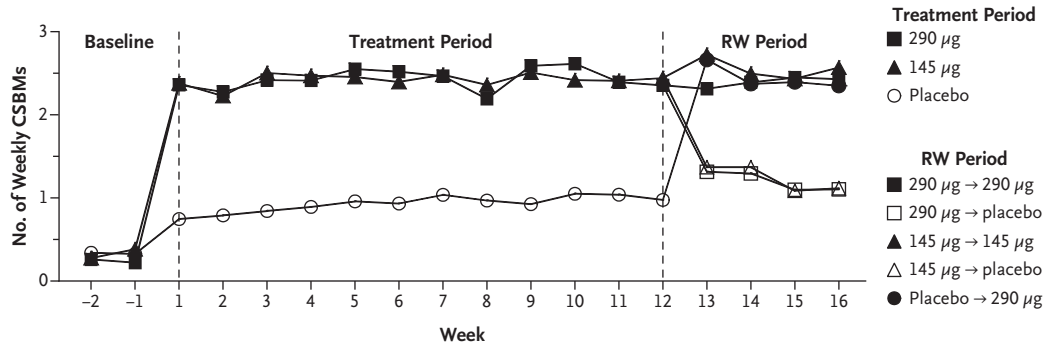

Figure 2. Mean Number of Weekly Complete Spontaneous Bowel Movements (CSBMs) in Trial 303, According to Study Period.

Both the 145-μg and 290-μg doses of linaclotide resulted in a significant increase in the number of weekly CSBMs, as compared with placebo, which was observed during week 1 and was sustained across the 12-week treatment period and the 4-week randomized withdrawal (RW) period. Among the patients who were randomly reassigned to placebo during the RW period, the number of weekly CSBMs did not fall below the baseline level.

verse events. Other safety evaluations included physical examinations, electrocardiographic recordings, vital-sign measurements, and standard laboratory tests.

STATISTICAL ANALYSIS

On the basis of results from a previous phase 2b study,[18] we calculated that a sample of 200 patients per study group would provide more than 90% power to detect a difference in the primary end point. For each trial, the overall family-wise type I error rate for testing the primary and secondary efficacy end points was controlled at the 0.05 significance level with the use of a five-step, serial, gatekeeping, multiple-comparisons procedure. Secondary end points were analyzed with the use of an analysis-of-covariance (ANCOVA) model with fixed-effect terms for study group and geographic region and with the corresponding baseline value as a covariate. The change-from-baseline means are the least-squares means from the ANCOVA model, based on patients' overall average scores during the 12-week treatment period (except for SBMs and CSBMs, for which overall weekly rates were calculated). The end points of treatment satisfaction and treatment continuation were analyzed with the use of an analysis-of-variance model with fixed-effect terms for study group and geographic region. Dichotomous end points were analyzed with the use of a Cochran–Mantel–Haenszel test, controlling for geographic region. We used geographic region in the analyses, rather than trial center, because of the potential for trial centers to have small numbers of patients.

Patients were assumed not to have had bowel movements or not to have taken rescue medications if the corresponding daily question was not answered; missing values were not imputed for any other assessments. For the primary efficacy end point, if a patient dropped out of the trial or otherwise did not report CSBM frequency data for a particular week during the treatment period, the patient was not considered to have had a response (i.e., three or more CSBMs and an increase of at least one CSBM from baseline) during that week. For the change-from-baseline secondary end points, an observed-cases approach to missing data was applied — that is, if a patient dropped out of the study or otherwise did not report data, the average of the nonmissing data obtained during the 12-week treatment period was considered the patient's 12-week value. All reported P values are based on two-sided tests.

All patients from both trials who took at least one dose of the study medication were included in pooled safety analyses (the safety population). Efficacy analyses were based on a modified intention-to-treat principle, with the intention-to-treat population defined as patients in the safety population who had at least one post-randomization entry for the primary efficacy assessment. The statistical analyses of the efficacy data sets (spe-

Table 2. Secondary and Additional End Points (Intention-to-Treat Population).*

End Point	Trial 303					Trial 01				
	Placebo (N=209)	Linaclotide, 145-μg Dose (N=217)	P Value	Linaclotide, 290-μg Dose (N=216)	P Value	Placebo (N=215)	Linaclotide, 145-μg Dose (N=213)	P Value	Linaclotide, 290-μg Dose (N=202)	P Value
CSBMs										
Mean no./wk	0.9	2.4		2.4		0.9	2.2		2.9	
Change from baseline no./wk	0.5	1.9	<0.001	2.0	<0.001	0.6	2.0	<0.001	2.7	<0.001
CSBM ≤24 hr after first dose (% of patients)†	11.0	33.2	<0.001	26.9	<0.001	13.5	28.2	<0.001	29.7	<0.001
Increase of ≥1 CSBM for 9 of 12 wk (% of patients)†	11.0	39.2	<0.001	37.0	<0.001	13.0	31.0	<0.001	40.1	<0.001
SBMs										
Mean no./wk	3.2	5.2		5.1		3.0	5.3		5.6	
Change from baseline no./wk	1.1	3.0	<0.001	3.0	<0.001	1.1	3.4	<0.001	3.7	<0.001
SBM ≤24 hr after first dose (% of patients)†	39.7	70.0	<0.001	54.6	0.001	39.1	64.3	<0.001	60.4	<0.001
Increase of ≥2 SBMs for 9 of 12 wk (% of patients)†	12.9	41.0	<0.001	37.0	<0.001	16.3	39.0	<0.001	46.0	<0.001
Stool consistency										
Mean BSFS score‡	3.0	4.3		4.3		2.9	4.2		4.4	
Change from baseline score	0.6	1.9	<0.001	1.8	<0.001	0.6	1.8	<0.001	2.0	<0.001
Straining severity										
Mean straining score§	2.7	2.1		2.1		2.7	2.1		2.0	
Change from baseline score	−0.5	−1.1	<0.001	−1.2	<0.001	−0.6	−1.1	<0.001	−1.2	<0.001
Abdominal discomfort										
Mean discomfort score§	2.2	2.0		2.1		2.3	2.0		2.0	
Change from baseline score	−0.3	−0.5	<0.001	−0.4	0.006	−0.3	−0.5	<0.001	−0.5	<0.001
Decrease of ≥0.5 points in score for 9 of 12 wk (% of patients)†	21.1	33.6	0.003	31.9	0.01	20.5	29.1	0.04	35.1	0.001

Bloating										
Mean bloating score§	2.5	2.3		2.4		2.6	2.3		2.3	
Change from baseline score	−0.2	−0.5	<0.001	−0.4	0.005	−0.2	−0.4	<0.001	−0.5	<0.001
Decrease of ≥0.5 points in score for 9 of 12 wk (% of patients)†	15.3	30.0	<0.001	27.8	0.002	17.7	29.1	0.006	32.7	<0.001
Constipation severity										
Mean score§	3.0	2.3		2.5		3.0	2.4		2.3	
Change from baseline score	−0.27	−0.90	<0.001	−0.81	<0.001	−0.31	−0.91	<0.001	−0.95	<0.001
Decrease of ≥1 point in score for 9 of 12 wk (% of patients)†	17.2	39.2	<0.001	35.2	<0.001	16.7	35.2	<0.001	38.1	<0.001
Constipation relief										
Mean score¶	3.6	2.6		2.8		3.4	2.8		2.6	
Change from baseline score†	−0.39	−1.30	<0.001	−1.19	<0.001	−0.57	−1.22	<0.001	−1.37	<0.001
Relief of constipation symptoms (% of patients)†‖	16.7	54.8	<0.001	46.8	<0.001	19.5	39.9	<0.001	47.0	<0.001
Treatment satisfaction, wk 12										
Mean score**	2.0	3.3	<0.001	3.1	<0.001	2.3	3.1	<0.001	3.4	<0.001
Quite or very satisfied (% of patients)†	14.8	49.3	<0.001	40.7	<0.001	22.8	41.8	<0.001	53.0	<0.001
Treatment continuation, wk 12										
Mean score††	3.0	3.8	<0.001	3.6	<0.001	3.2	3.6	0.03	3.7	0.002
Quite or very likely to continue treatment (% of patients)†	46.4	64.5	<0.001	57.4	0.03	50.2	57.7	0.14	61.9	0.023

* P values are for the comparison of each of the linaclotide groups with the placebo group; all P values were calculated with the use of analysis of covariance (ANCOVA), unless otherwise noted. Changes from baseline are the least-squares means obtained with the use of the ANCOVA model. BSFS denotes Bristol Stool Form Scale, CSBM complete spontaneous bowel movement, and SBM spontaneous bowel movement.
† P values were calculated with the use of the Cochran–Mantel–Haenszel test.
‡ Scores for BSFS range from 1 to 7, with higher scores indicating softer stools.
§ Scores for straining severity, abdominal discomfort, bloating, and constipation severity range from 1 to 5, with higher scores indicating more straining.
¶ Scores for constipation relief range from 1 to 7, with 1 indicating complete relief, 4 no change, and 7 very severe constipation.
‖ Responses regarding the relief of constipation were "somewhat relieved," "considerably relieved," or "completely relieved" for 100% of the weekly scores and "considerably relieved" or "completely relieved" for at least 50% of the weekly scores.
** Scores for treatment satisfaction ranged from 1 to 5, with 1 indicating not at all satisfied and 5 very satisfied.
†† Scores for treatment continuation ranged from 1 to 5, with 1 indicating not at all likely and 5 very likely.

cifically primary and secondary end points) were independently confirmed. (The statistical-analysis plan is provided at NEJM.org.)

RESULTS

PATIENTS

Of the 2379 patients in both trials who signed consent forms, 1276 were randomly assigned to one of three study groups and received at least one dose of trial medication (the safety population) (see Fig. 1 in the Supplementary Appendix, available at NEJM.org). Four patients who received at least one dose of the assigned study medication did not report any post-randomization CSBMs, the primary efficacy assessment (1 patient in Trial 303 and 3 patients in Trial 01). Thus, 1272 patients were included in the intention-to-treat analysis (642 in Trial 303 and 630 in Trial 01). The study groups were well balanced with respect to demographic characteristics, baseline bowel and abdominal symptoms, and constipation severity (Table 1). Rates of compliance with daily assessments made by means of the interactive voice-response system during the treatment period were 88.3% and 86.3% in Trials 303 and 01, respectively.

PRIMARY EFFICACY END POINT

In Trials 303 and 01, respectively, 21.2% and 16.0% of the patients who received the 145-μg dose of linaclotide and 19.4% and 21.3% of the patients who received the 290-μg dose of linaclotide met the primary end point of both three or more CSBMs per week and an increase of one or more CSBM per week from baseline for at least 9 of 12 weeks, as compared with 3.3% and 6.0% of the patients who received placebo ($P<0.01$ for each linaclotide dose, as compared with placebo, for each trial) (Fig. 1). During each week of the treatment period, the proportion of patients in both trials who had both three or more CSBMs per week and an increase of one or more CSBM per week from baseline was significantly greater for both doses of linaclotide than for placebo. In both trials, differences in the overall response rates between the two linaclotide groups (the 145-μg dose vs. the 290-μg dose) were not significant ($P=0.63$ for Trial 303 and $P=0.19$ for Trial 01).

Sensitivity analyses included data for all the patients (including the four patients who received at least one dose of trial medication but did not provide any post-randomization CSBM assessments and were classified as having no response) and revealed similar results.

SECONDARY EFFICACY END POINTS

Linaclotide-treated patients had significant improvements from baseline to week 12 in all secondary end points, as compared with patients who received placebo, including changes in bowel symptoms (number of weekly CSBMs [Fig. 2] and SBMs, stool consistency, and straining severity), abdominal symptoms (discomfort and bloating), and constipation severity (Table 2).

ADDITIONAL EFFICACY END POINTS

Beginning at week 1 and for every week during the 12-week treatment period, the weekly CSBM rates increased significantly with linaclotide treatment, as compared with placebo, and the increases were maintained throughout the 12-week treatment period (Fig. 2). For each trial, scores for constipation relief, treatment satisfaction, and treatment continuation were also significantly greater in the linaclotide groups than in the placebo group (Table 2).

CONSTIPATION-RELATED QUALITY OF LIFE

At week 12 in Trials 303 and 01, respectively, 44.9% and 42.2% of patients who received the 145-μg dose of linaclotide and 35.5% and 46.8% of those who received the 290-μg dose of linaclotide had an improvement of 1 point or more from baseline in the overall PAC-QOL score, as compared with 18.7% and 27.8% of patients who received placebo ($P<0.01$ for each linaclotide dose, as compared with placebo, in both trials). Improvements in the overall and component PAC-QOL scores were significantly greater with both linaclotide doses in each trial, as compared with placebo (with the exception of psychosocial discomfort in Trial 303 for patients given the 290-μg dose) (Fig. 2 in the Supplementary Appendix).

RANDOMIZED WITHDRAWAL

The patients who continued to take linaclotide and those who switched from placebo to linaclotide had sustained increases in the rate of CSBMs during the randomized withdrawal period that were similar to the levels reported during the treatment period (Fig. 2); the patients who switched from linaclotide to placebo had a decreased rate of CSBMs, which was similar to the rates in the placebo groups during the treatment period. There

was no evidence of "rebound" (i.e., fewer CSBMs or worsening of other constipation symptoms), as compared with baseline levels.

POOLED SAFETY DATA

The most common adverse event was diarrhea (Table 3). A single death reported during the trials was due to an overdose of fentanyl. Serious adverse events were reported in 1.4% of patients receiving 145 μg of linaclotide, 2.6% of patients receiving 290 μg of linaclotide, and 2.1% of patients receiving placebo (Table 1 in the Supplementary Appendix). During the 12-week treatment period, discontinuation of treatment owing to adverse events was higher among the linaclotide-treated patients, occurring in 7.9% of patients who received 145 μg and in 7.3% of those who received 290 μg of linaclotide, as compared with 4.2% of patients receiving placebo, and was primarily a result of an increased rate of discontinuation because of diarrhea in those groups (4.7% and 3.8% of those who received 145 μg and 290 μg of linaclotide, respectively, vs. 0.5% in the placebo group). For most of the patients, the first occurrence of diarrhea was reported during the initial 2 weeks of therapy (accounting for 61.7% of all patients with an episode of diarrhea during the 12-week treatment period). A total of 13 of the 852 patients (1.5%) who received linaclotide had diarrhea that was graded by the investigator as severe, as compared with 1 of 424 patients (0.2%) who received placebo. There were no clinically significant differences in hematologic results or blood chemical values, findings on urinalysis, electrocardiographic results, or vital signs between the linaclotide and placebo groups.

Table 3. Adverse Events during Treatment (Combined Safety Populations in Trials 303 and 01).*

Adverse Event	Placebo (N=424)	Linaclotide	
		145-μg Dose (N=430)	290-μg Dose (N=422)
		no. of patients (%)	
Any event	221 (52.1)	260 (60.5)	235 (55.7)
Diarrhea	20 (4.7)	69 (16.0)	60 (14.2)
Flatulence	22 (5.2)	24 (5.6)	21 (5.0)
Abdominal pain	13 (3.1)	17 (4.0)	20 (4.7)
Abdominal distention	10 (2.4)	15 (3.5)	15 (3.6)
Upper respiratory infection	17 (4.0)	22 (5.1)	13 (3.1)
Nasopharyngitis	13 (3.1)	9 (2.1)	17 (4.0)
Sinusitis	8 (1.9)	13 (3.0)	11 (2.6)
Upper abdominal pain	7 (1.7)	13 (3.0)	5 (1.2)

* Data are shown for adverse events that were reported in at least 3% of patients in either linaclotide group and for events that were reported in a higher proportion of patients in either linaclotide group than in the placebo group.

DISCUSSION

In these two large phase 3 clinical trials involving patients with chronic constipation, linaclotide significantly increased the percentage of patients who reached the primary end point of three or more CSBMs per week, with an increase from baseline of at least one CSBM per week for 9 or more weeks of the 12-week treatment period.[4] This response end point required that patients have normalization of bowel function (i.e., three or more CSBMs per week) for at least 75% of the treatment period. Because of the rigor of the primary end point, only about 20% of the patients who received linaclotide and 5% of those who received placebo were considered to have had a response. Of perhaps greater clinical relevance, the mean stool frequency in the two trials increased to 5.1 and 5.6 SBMs per week and to 2.2 and 2.9 CSBMs per week in the linaclotide-treated patients, as compared with 3.0 and 3.2 SBMs per week and 0.9 and 0.9 CSBMs per week in the placebo-treated patients.

In addition to improving stool frequency, linaclotide significantly improved stool consistency, reduced straining, and reduced abdominal symptoms (bloating and discomfort), which are often reported to be bothersome to patients with chronic constipation.[4] The effects of linaclotide on symptoms of constipation were observed within the first 24 hours and were sustained through 16 weeks. Linaclotide also significantly improved treatment satisfaction, reduced the severity of constipation, and improved disease-related quality of life. Although the improvement in bowel function with linaclotide treatment is most likely a consequence of increased luminal fluid, with an acceleration of intestinal transit, additional mechanisms may contribute to the improvement in abdominal symptoms. In fact, linaclotide has been shown to reduce visceral hypersensitivity in animal models by means of a guanylate cyclase C–cGMP mechanism.[9]

The observation that diarrhea occurred more commonly with linaclotide than with placebo is

not surprising, since diarrhea is an extension of linaclotide's pharmacologic effects. In this trial, episodes of diarrhea were mostly mild or moderate in severity; treatment had to be discontinued because of diarrhea in 4.2% of linaclotide-treated patients as compared with 0.5% of patients receiving placebo. Long-term studies are needed to assess the safety of long-term treatment with this drug.

In conclusion, in these two, large phase 3 trials involving patients with chronic constipation, linaclotide led to improvement in bowel and abdominal symptoms and reduced the severity of constipation. Linaclotide has the potential to offer multisymptom relief to patients with chronic constipation.

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