Abdominal Pain Response to Rifaximin in Patients With Irritable Bowel Syndrome With Diarrhea

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INTRODUCTION: **Abdominal pain is the principal symptom of irritable bowel syndrome (IBS). This analysis examined abdominal pain response in adults with IBS with diarrhea (IBS-D) receiving the nonsystemic antibiotic rifaximin.**

METHODS: **In the Targeted Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for IBS-D 3 trial, adults with IBS-D received open-label rifaximin 550 mg 3 times daily for 2 weeks, followed by the 4-week post-treatment phase assessing abdominal pain and stool consistency response. Responders were followed for up to 18 additional weeks; patients with recurrence were randomly assigned to receive two 2-week courses of double-blind rifaximin 550 mg 3 times daily or placebo, separated by 10 weeks. Analyses evaluated mean weekly improvements from baseline (e.g., ≥30%, ≥40%, and ≥50%) in abdominal pain during the 4-week post–repeat-treatment phases.**

RESULTS: **Of the 2,438 evaluable patients, 1,384 (56.8%) had abdominal pain response to open-label rifaximin (≥30% improvement from baseline in the mean weekly abdominal pain score during ≥2 of the first 4 weeks post-treatment). Weekly decrease (improvement) in responders' mean abdominal pain score (scale range, 0–10) from baseline ranged from −2.6 to −3.3 points during the 18-week follow-up. After the first double-blind repeat treatment, a significantly higher percentage of rifaximin-treated patients were abdominal pain responders (53.9% [172/319]) vs placebo (44.4% [134/302], $P = 0.02$), with similar results after the second repeat treatment (52.9% [155/293] vs 44.7% [123/275], respectively, $P = 0.047$). A significantly higher percentage of rifaximin-treated patients were weekly abdominal pain responders for ≥50% of the 18-week double-blind repeat treatment phase (47.9% [138/288] vs 35.9% [97/270], $P = 0.004$).**

DISCUSSION: **Rifaximin is efficacious in improving abdominal pain in adults with IBS-D.**

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional bowel disorder characterized by recurrent abdominal pain that is associated with changes in the frequency and/or appearance of stool (1). More than one-fifth of patients with IBS have IBS with diarrhea (IBS-D), characterized by >25% of bowel movements with Bristol Stool Form Scale (BSS) type 6 or 7 and <25% of bowel movements with BSS type 1 or 2 for ≥2 weeks (1,2). Recurrent abdominal pain and altered stool form are the key components of IBS (3); pain may occur anywhere in the abdomen, but crampy pain in the lower abdomen is common (1). Abdominal pain and symptom frequency (i.e., average 8 days/month) are common reasons patients seek health care (2). Alterations in the gut microbiota have been observed in patients with IBS compared with healthy individuals (4–7). The composition of the gut microbiota has been associated with abdominal pain in patients with IBS (8,9); interestingly, it has also been associated with abdominal pain in healthy individuals (10,11).

Therapies for IBS-D that may modulate the gut microbiota include antibiotics (12), such as the nonsystemic antibiotic rifaximin, which is approved by the US Food and Drug Administration (FDA) for the treatment of IBS-D in adults (13–15). Several trials have evaluated the efficacy of rifaximin for the treatment of IBS (16–19). A meta-analysis of 5 studies (n = 1,803 patients) determined that rifaximin significantly improved global IBS symptoms compared with placebo (odds ratio: 1.6; 95% confidence interval [CI]: 1.2–2.0, $P < 0.001$) (12). In addition, rifaximin has been shown to be efficacious and well tolerated as repeat treatment for patients with IBS symptom recurrence (20–23), including a randomized clinical study (Targeted Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for IBS-D [TARGET] 3) of patients with IBS-D (21). In TARGET 3, for the

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primary composite endpoint, a significantly higher percentage of patients with symptom recurrence, treated with a repeat course of rifaximin, simultaneously experienced a ≥30% improvement from baseline in abdominal pain and a ≥50% decrease from baseline in the frequency of loose/watery stool vs those who received a course of placebo (38.1% vs 31.5%, $P = 0.03$) (21). The aim of this analysis was to further characterize the impact of a single course and 2 repeated 2-week courses of rifaximin on abdominal pain in patients with IBS-D.

METHODS

Study design and patients

The patient population and study design have been described previously (21). Briefly, adults with IBS (diagnosed based on the Rome III criteria) who, during a 2-week placebo screening phase, rated their mean abdominal pain as ≥3 (scale range, 0–10) and bloating as ≥3 (scale range, 0–6) and had ≥2 days per week with BSS type 6 or 7 (mushy/watery) stool were eligible for inclusion. As previously described, all institutional review boards and ethics committees at participating study sites approved the study protocol (21). Written informed consent was obtained from all patients (21).

The study design included an open-label treatment phase and a double-blind, placebo-controlled treatment phase (Figure 1) (21). During the open-label treatment phase, patients received a 2-week course of open-label rifaximin 550 mg 3 times daily (t.i.d.), followed by a 4-week treatment-free period to assess rifaximin response. Composite responders (i.e., patients simultaneously meeting weekly response criteria for abdominal pain [≥30% decrease from baseline in the mean weekly pain score] and stool consistency [≥50% decrease from baseline in number of days/week with BSS type 6 or 7 stool] for ≥2 of the first 4 weeks after treatment) were observed for up to an additional 18 weeks (total observation period, 22 weeks). Patients who did not meet the definition of response during this open-label treatment phase were discontinued from the study. Responders who experienced recurrence of IBS-D symptoms (i.e., loss of response for either weekly abdominal pain or stool consistency for ≥3 weeks of a consecutive ongoing 4-week period) entered into the double-blind treatment phase and were randomly assigned to receive two 2-week courses of treatment with rifaximin 550 mg t.i.d. or placebo in a double-blind manner. The 2 courses were separated by 10 weeks, and the second treatment course was administered regardless of the response status (21). Response was assessed during the 4 weeks after each treatment (21).

Assessments

The primary composite endpoint of the original study was the percentage of patients who were responders (i.e., patients simultaneously meeting weekly response criteria of a ≥30% decrease from baseline in the mean weekly pain score and a ≥50% decrease from baseline in number of days/week with BSS type 6 or 7 stool) for ≥2 of the first 4 weeks after the first double-blind treatment (primary evaluation period; Figure 1) (21). Abdominal pain scores were evaluated daily by patient response to the question, "In regards to your specific IBS symptom of abdominal pain, on a scale of 0 ('no pain at all') to 10 ('worst possible pain'), what was your

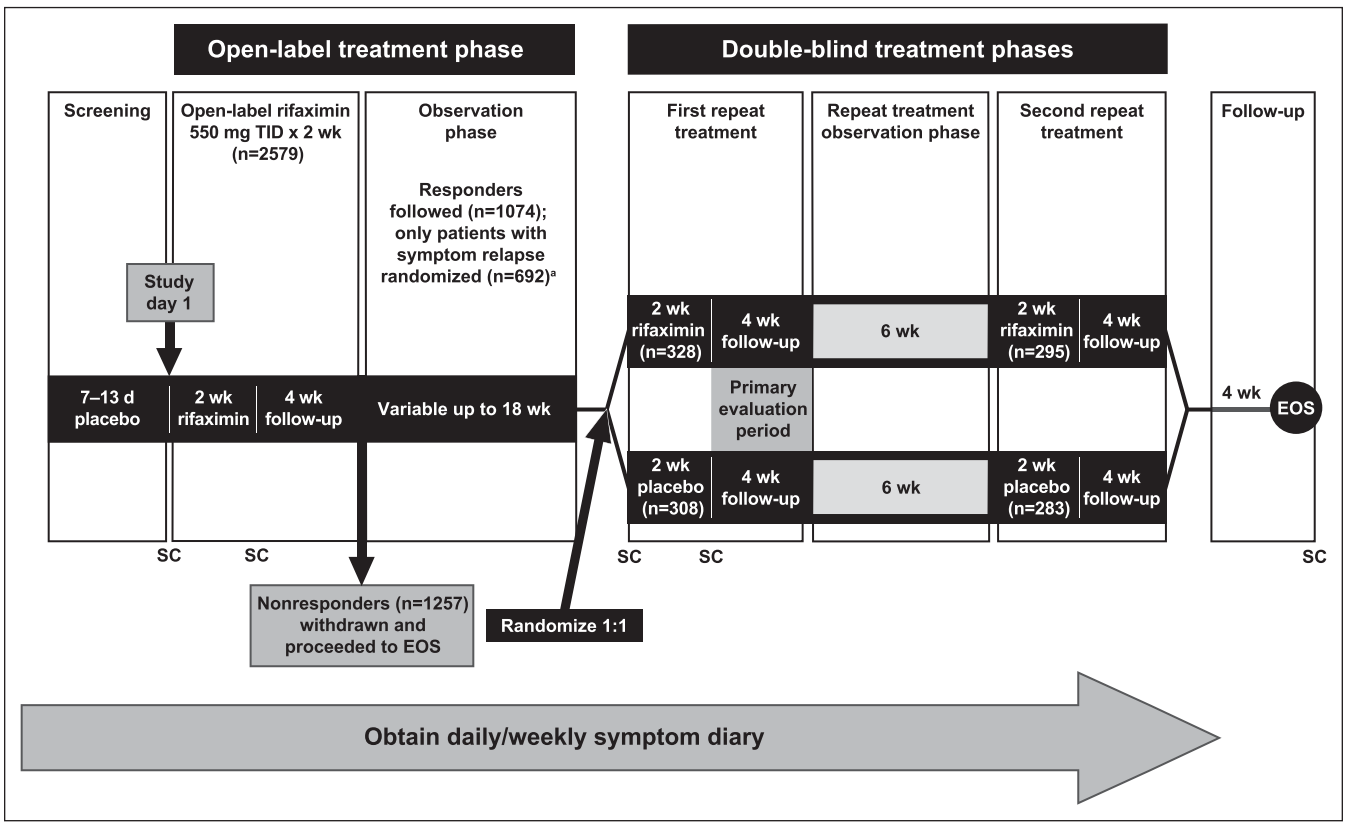

Figure 1. Study design. EOS, end of study; SC, stool sample collection time point; t.i.d., 3 times daily. [a]Fifty-six patients were not randomized because of enrollment closure. Adapted with permission from Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2016;151(6):1113–21 (21).

worst IBS-related abdominal pain over the last 24 hours?" These data were used to determine the weekly response rates, as defined below.

Several definitions of abdominal pain response were examined by altering the threshold percentage for improvement and duration of response after an open-label and double-blind treatment. Abdominal pain response was assessed using cutoffs of ≥30%, ≥40%, ≥50%, or ≥60% improvement from open-label baseline, cutoffs of ≥30%, ≥40%, ≥50%, ≥60%, ≥70%, ≥80%, ≥90%, or 100% improvement from double-blind baseline, and/or by number of weeks of meeting the criterion (i.e., ≥2 of the first 4 weeks post-treatment, ≥3 of the first 4 weeks post-treatment, or 4 of the first 4 weeks post-treatment). Durable response in the double-blind treatment phase was defined as maintenance of response (assessed in the primary evaluation period) during the following 6 weeks of the observation phase (i.e., 10 weeks post-treatment). In this analysis, double-blind response in patients was analyzed by double-blind baseline abdominal pain scores (i.e., mean abdominal pain score during the past 2 weeks of the 18-week open-label observation phase). The overall median first double-blind baseline abdominal pain score, which was calculated as 4.6, was used to divide patients into 2 groups (i.e., one group with a baseline abdominal pain score <4.6 and one group with a score ≥4.6).

Statistical analyses

Data were analyzed using last observation carried forward (LOCF; patients missing weekly responses were replaced with the last nonmissing postbaseline weekly response) or observed case (OC; patients with insufficient data available to determine efficacy [e.g., responder or nonresponder] for the particular assessment period were excluded) methodology. Data obtained in the open-label 18-week observation phase were analyzed using the Cochran–Mantel–Haenszel test, accounting for analysis center and time to recurrence. In the double-blind treatment phase, P values based on χ^2 were used to compare differences between treatments based on outcomes of various definitions of abdominal pain response.

RESULTS

Open-label treatment phase

A total of 2,579 patients with IBS-D received open-label rifaximin (21). Of the 2,438 evaluable patients, 1,384 (56.8%) were abdominal pain responders (21). Demographic and baseline disease characteristics were generally comparable among the overall population, abdominal pain responders, and abdominal pain nonresponders (Table 1) (21). Of the 1,384 abdominal pain responders (≥30% improvement from baseline for ≥2 of the first 4 weeks post-treatment), 1,074 (i.e., 44.1% of 2,438 evaluable patients) met the original composite endpoint of the study and were eligible to continue in the up to 18-week, treatment-free observation phase (21). Of the 1,074 abdominal pain responders (component of the original 2-point composite endpoint), 382 (35.6%) did not experience recurrence of abdominal pain during the 18-week observation phase.

During the 18-week observation phase, the mean decrease (improvement) from open-label baseline (mean, 5.5 points) in average weekly abdominal pain scores, based on daily diary entries, ranged from −2.6 to −3.3 points (Figure 2). For the abdominal pain responder population with recurrence of abdominal pain during the open-label treatment phase, the median time to recurrence was 14.0 weeks. The percentage of abdominal pain responders decreased as the threshold for defining improvement from baseline increased (i.e., ≥40% to ≥60% improvement from baseline; Figure 3); for patients with improvement from baseline for ≥2 of the first 4 weeks, the mean percentage of abdominal pain responders decreased from 48.3% to 30.8%, with an increase in the threshold from ≥40% to ≥60% improvement from baseline. Furthermore, as the threshold for weekly duration of response post-treatment decreased (i.e., all 4 weeks to ≥2 of the first 4 weeks; Figure 3), the percentage of abdominal pain responders increased (e.g., at the ≥40% threshold, the percentage of abdominal pain responders increased from 27.4% [all 4 weeks] to 48.3% [≥2 of the first 4 weeks]).

Double-blind treatment phase

In the double-blind treatment phase, a total of 328 and 308 patients were randomly assigned to receive up to 2 courses of double-blind rifaximin or placebo, respectively (21). As reported in the original study (21), their mean daily baseline abdominal pain score on entering the double-blind treatment phase (4.5 [95% CI: 4.4–4.7]) was lower than observed at open-label baseline before rifaximin treatment (5.6 [95% CI: 5.5–5.7]). During the first 4 weeks after the first course of repeat treatment (primary evaluation period), a significantly higher percentage of patients were abdominal pain responders (≥30% improvement from baseline in abdominal pain score for ≥2 of the first 4 weeks post-treatment) in the rifaximin group using OC (53.9% vs 44.4%, $P = 0.02$) or LOCF (51.8% vs 42.5%, $P = 0.02$; Table 2) methodologies. The percentage of patients with abdominal pain response decreased as the threshold for definition of response was modified from ≥30% to ≥50% for ≥2 of the first 4 weeks post-treatment (Table 3): from 51.8% to 32.3% with rifaximin and from 42.5% to 28.6% with placebo. Differences between the 2 treatment groups were not significant at greater thresholds for improvement (≥40% and higher) and when the time frame of response was increased (≥2, ≥3, or 4 of the first 4 weeks; Table 3) at these thresholds. However, significant differences in the durability of response (additional 6 weeks post-treatment) were observed for abdominal pain responders with ≥30% improvement from baseline in abdominal pain score for ≥2, ≥3, and 4 of the first 4 weeks post-treatment in the rifaximin group vs placebo (≥2 weeks: 37.5% vs 26.3%, respectively, $P = 0.003$; ≥3 weeks: 32.6% vs 23.1%, $P = 0.008$; and 4 weeks: 24.7% vs 17.2%, $P = 0.03$; Table 3). Furthermore, the percentage of patients with durability of response with rifaximin differed significantly from placebo with a threshold of abdominal pain response of ≥40% improvement from baseline for ≥2 of the first 4 weeks post-treatment (29.0% vs 20.5%, respectively, $P = 0.01$).

After the second repeat treatment, a significantly higher percentage of patients in the rifaximin group were abdominal pain responders compared with placebo (52.9% vs 44.7%, $P = 0.047$) using OC methodology; however, the difference was not significant using LOCF methodology ($P = 0.055$; Table 2). When considering abdominal pain response to both repeat treatment courses, significantly more patients in the rifaximin group were abdominal pain responders after each course compared with placebo (Table 2). In addition, a significantly higher percentage of patients in the rifaximin group were abdominal pain responders for ≥50% of the 18 weeks in the

Table 1. Demographic and baseline disease characteristics (open-label treatment phase)

Parameter	Overall population (N = 2,579)[a]	Abdominal pain responders[b] (n = 1,384)[c]	Abdominal pain nonresponders (n = 1,054)[c]
Age, yr, mean (SD)	46.4 (13.7)	47.0 (13.8)	45.7 (13.5)
Female, n (%)	1,760 (68.2)	952 (68.8)	709 (67.3)
Race, n (%)			
White	2,155 (83.6)	1,177 (85.0)	857 (81.3)
Black	289 (11.2)	129 (9.3)	146 (13.9)
Other	135 (5.2)	78 (5.6)	51 (4.8)
Average daily bowel movements, mean (SD)	3.9 (2.2)	3.7 (2.0)	4.0 (2.4)
Duration since the first onset of IBS symptoms, yr, mean (SD)	10.9 (10.8)	11.4 (11.1)	10.1 (10.2)
Average daily score, mean (SD)			
Abdominal pain	5.5 (1.7)	5.5 (1.6)	5.6 (1.7)
Stool consistency	5.6 (0.8)	5.6 (0.8)	5.6 (0.9)
Bloating	4.1 (0.9)	4.1 (0.9)	4.1 (1.0)
IBS symptoms	4.2 (0.9)	4.1 (0.9)	4.2 (0.9)

IBS, irritable bowel syndrome.
[a]Data from Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2016;151(6):1113–21 (21).
[b]Abdominal pain responders defined as patients with a ≥30% improvement from baseline in the mean weekly abdominal pain score during ≥2 weeks of the first 4 weeks post-treatment.
[c]One hundred forty-one patients were excluded because of insufficient data to determine response (i.e., observed case methodology).

repeat treatment phase of the study (i.e., from week 1 of the first repeat treatment course through 4 weeks after the second repeat treatment course [Table 2]).

Subgroup analyses by age and sex in patients with abdominal pain response after the first repeat treatment course were conducted (Table 2). Significant differences with rifaximin vs placebo

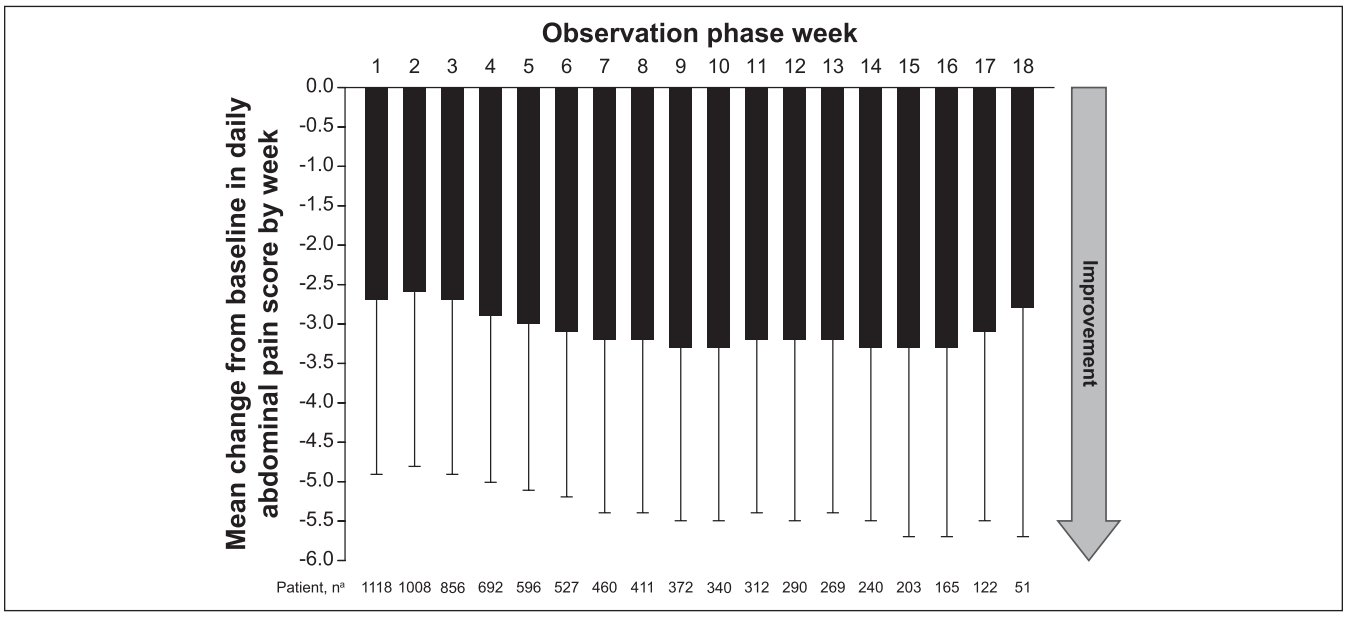

Figure 2. Mean improvement in average daily abdominal pain score by week in evaluable abdominal pain responders (open-label treatment phase).[a]Data may not have been available for multiple reasons, including patient experiencing stool consistency relapse (<50% decrease from baseline in number of days/week with the Bristol Stool Form Scale type 6 or 7 for ≥3 weeks of a consecutive on going 4-week period) and proceeding into the double-blind treatment phase or randomization to double-blind treatment phase closed by sponsor. [b]Patients with ≥30% improvement from baseline in the mean weekly abdominal pain score during ≥2 weeks of the first 4 weeks post-treatment. Error bars represent SD.

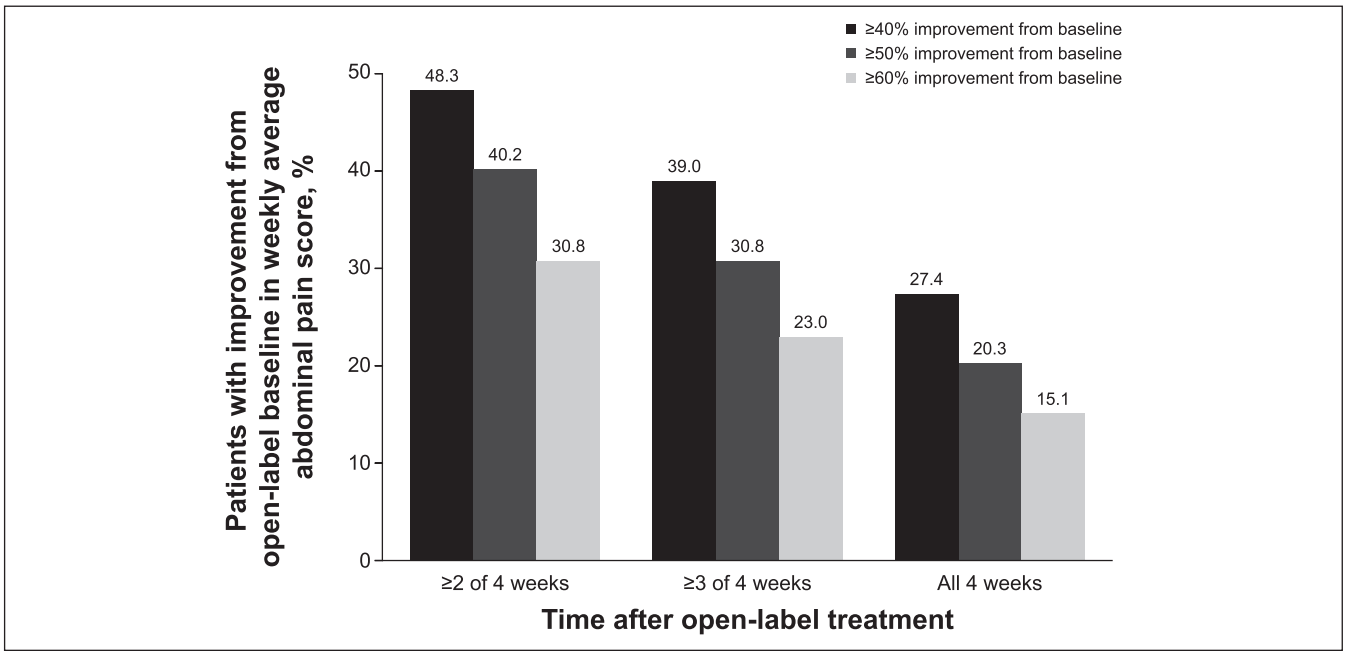

Figure 3. Mean improvement from baseline in average weekly abdominal pain score by responder threshold (open-label treatment phase).

in LOCF analysis were observed in patients 65 years or older ($P = 0.04$) and in women ($P = 0.03$); in the OC analysis, significant differences with rifaximin vs placebo were observed in patients younger than 65 years ($P = 0.04$) and in women ($P = 0.04$). In a subgroup analysis of patients with double-blind baseline abdominal pain scores of <4.6 and ≥4.6, demographics were generally similar between the 2 populations (Table 4); however, in addition to average daily abdominal pain scores, average daily bowel movements and IBS severity were greater in patients with baseline abdominal pain scores of ≥4.6. A significantly higher percentage of patients with a baseline abdominal pain score of <4.6 who received rifaximin were responders for both abdominal pain and stool consistency (original study composite endpoint) vs placebo (35.2% vs 24.5%, $P = 0.04$, LOCF; Table 5). Abdominal pain and stool consistency response were numerically greater with rifaximin in the population with a baseline abdominal pain score of ≥4.6 compared with placebo (35.6% vs 26.8%, $P = 0.09$, LOCF; Table 5). In addition, for patients with double-blind baseline

Table 2. Abdominal pain responder[a] analyses in the double-blind treatment phase

	OC			LOCF		
Population, % (n/n)	**Rifaximin**	**Placebo**	***P* value**	**Rifaximin**	**Placebo**	***P* value**
First repeat treatment	53.9 (172/319)	44.4 (134/302)	0.02	51.8 (170/328)	42.5 (131/308)	0.02
Second repeat treatment	52.9 (155/293)	44.7 (123/275)	0.047	52.5 (155/295)	44.9 (127/283)	0.055
First and second repeat treatment courses	42.0 (123/293)	29.7 (83/279)	0.002	41.7 (123/295)	30.7 (87/283)	0.005
≥50% of 18 wk in the double-blind treatment phase[b]	47.9 (138/288)	35.9 (97/270)	0.004	46.8 (138/295)	35.3 (100/283)	0.004
Subgroup						
Age						
<65 yr	53.4 (150/281)	44.5 (122/274)	0.04	52.2 (151/289)	44.1 (123/279)	0.05
≥65 yr	57.9 (22/38)	42.9 (12/28)	0.06	59.0 (23/39)	41.4 (12/29)	0.04
Sex						
Female	53.2 (115/216)	42.3 (91/215)	0.04	52.7 (117/222)	41.6 (91/219)	0.03
Male	55.3 (57/103)	49.4 (43/87)	0.40	53.8 (57/106)	49.4 (44/89)	0.51

LOCF, last observation carried forward; OC, observed case.
[a]Patients with a ≥30% improvement from baseline in weekly abdominal pain score for ≥2 of the first 4 weeks post-treatment.
[b]Abdominal pain responders for ≥50% of the weeks from week 1 of the first repeat treatment course through 4 weeks after the second repeat treatment course (i.e., 18 weeks).

Table 3. Responders by abdominal pain improvement threshold[a] in the double-blind treatment phase

Definition of abdominal pain response	Responders, n (%)		Responders with durable response,[b] n (%)	
	Rifaximin (n = 328)	Placebo (n = 308)	Rifaximin (n = 328)	Placebo (n = 308)
≥30% improvement from baseline[c]				
≥2 of 4 wk	170 (51.8)[d]	131 (42.5)	123 (37.5)[e]	81 (26.3)
≥3 of 4 wk	131 (39.9)	102 (33.1)	107 (32.6)[f]	71 (23.1)
4 of 4 wk	94 (28.7)	67 (21.8)	81 (24.7)[g]	53 (17.2)
≥40% improvement from baseline[c]				
≥2 of 4 wk	137 (41.8)	111 (36.0)	95 (29.0)[h]	63 (20.5)
≥3 of 4 wk	104 (31.7)	82 (26.6)	82 (25.0)	57 (18.5)
4 of 4 wk	69 (21.0)	51 (16.6)	60 (18.3)	40 (13.0)
≥50% improvement from baseline[c]				
≥2 of 4 wk	106 (32.3)	88 (28.6)	63 (19.2)	52 (16.9)
≥3 of 4 wk	77 (23.5)	61 (19.8)	53 (16.2)	44 (14.3)
4 of 4 wk	52 (15.9)	41 (13.3)	39 (11.9)	31 (10.1)
≥60% improvement from baseline[c]				
≥2 of 4 wk	85 (25.9)	64 (20.8)	53 (16.2)	34 (11.0)
≥3 of 4 wk	57 (17.4)	42 (13.6)	42 (12.8)	25 (8.1)
4 of 4 wk	39 (11.9)	31 (10.1)	29 (8.8)	19 (6.2)
≥70% improvement from baseline[c]				
≥2 of 4 wk	59 (18.0)	46 (14.9)	34 (10.4)	24 (7.8)
≥3 of 4 wk	37 (11.3)	33 (10.7)	26 (7.9)	17 (5.5)
4 of 4 wk	24 (7.3)	19 (6.2)	18 (5.5)	11 (3.6)
≥80% improvement from baseline[c]				
≥2 of 4 wk	35 (10.7)	30 (9.7)	17 (5.2)	16 (5.2)
≥3 of 4 wk	22 (6.7)	24 (7.8)	13 (4.0)	14 (4.5)
4 of 4 wk	11 (3.4)	9 (2.9)	9 (2.7)	7 (2.3)
≥90% improvement from baseline[c]				
≥2 of 4 wk	19 (5.8)	20 (6.5)	10 (3.0)	9 (2.9)
≥3 of 4 wk	8 (2.4)	12 (3.9)	5 (1.5)	7 (2.3)
4 of 4 wk	5 (1.5)	4 (1.3)	2 (0.6)	4 (1.3)
100% improvement from baseline[c]				
≥2 of 4 wk	11 (3.4)	14 (4.5)	5 (1.5)	6 (1.9)
≥3 of 4 wk	7 (2.1)	11 (3.6)	3 (0.9)	5 (1.6)
4 of 4 wk	5 (1.5)	6 (1.9)	1 (0.3)	3 (1.0)

[a]Last observation carried forward.
[b]Response maintained for an additional 6 weeks after the 4-week primary evaluation period (10 weeks post-treatment).
[c]Double-blind baseline.
[d]$P = 0.02$.
[e]$P = 0.003$.
[f]$P = 0.008$.
[g]$P = 0.03$.
[h]$P = 0.01$.

Table 4. Demographic and double-blind baseline disease characteristics by treatment for baseline abdominal pain score subgroups

Parameter	Baseline abdominal pain score <4.6		Baseline abdominal pain score ≥4.6	
	Rifaximin 550 mg t.i.d. (n = 165)	Placebo (n = 155)	Rifaximin 550 mg t.i.d. (n = 163)	Placebo (n = 153)
Age, yr, mean (SD)	50.0 (14.1)	44.7 (14.0)	45.7 (13.9)	46.5 (13.6)
Female, n (%)	115 (69.7)	112 (72.3)	107 (65.6)	107 (69.9)
Race, n (%)				
White	150 (90.9)	139 (89.7)	123 (75.5)	123 (80.4)
Black	11 (6.7)	11 (7.1)	26 (16.0)	20 (13.1)
Other	4 (2.4)	5 (3.2)	14 (8.6)	10 (6.5)
Average daily bowel movements, mean (SD)	2.7 (1.4)	2.6 (1.3)	4.1 (2.3)	4.3 (2.3)
Average daily abdominal pain score, mean (SD)	3.0 (1.3)	2.8 (1.3)	6.2 (1.6)	6.1 (1.5)
IBS severity, n (%)				
IBS-QOL total score ≤40	24 (14.5)	24 (15.5)	76 (46.6)	65 (42.5)
IBS-QOL total score >40	141 (85.5)	131 (84.5)	86 (52.8)	88 (57.5)
Missing	0	0	1 (0.6)	0

IBS, irritable bowel syndrome; IBS-QOL, irritable bowel syndrome quality of life questionnaire; t.i.d., 3 times daily.

abdominal pain scores <4.6 or ≥4.6, abdominal pain response (component of the original 2-point composite endpoint) was numerically greater with rifaximin vs placebo ($P > 0.05$), and those with an abdominal pain score of ≥4.6 who received rifaximin were significantly more likely to obtain durable abdominal pain response vs placebo ($P = 0.0496$; Table 5).

DISCUSSION

This analysis examined abdominal pain response in patients receiving up to three 2-week courses of rifaximin (1 open-label and 2 double-blind treatments). These results are clinically relevant because abdominal pain is present in patients with IBS-D more than one-third of days (mean duration of analysis, 72.9 days) (24), and abdominal pain commonly drives patients with IBS to seek medical care (2). Furthermore, IBS aberrantly affects employment, daily life activities, and quality of life (QOL) (2). The results of this analysis indicate that after a 2-week treatment with open-label rifaximin, 56.8% of patients with IBS-D were abdominal pain responders (i.e., ≥30% improvement from baseline in abdominal pain score for ≥2 of the first 4 weeks post-treatment). The maximum mean decrease from baseline (mean baseline score, 5.5 points; scale range, 0–10) in average weekly abdominal pain was −3.3 points, which is clinically meaningful (25). Furthermore, approximately one-third (35.6%) of these patients did not experience recurrence of abdominal pain for up to 22 weeks after a single 2-week course of rifaximin therapy. For patients with abdominal pain recurrence, the median time to recurrence was 3.5 months. In addition, after the first and second double-blind repeat treatments, a significantly higher percentage of patients receiving rifaximin were abdominal pain responders compared with placebo, suggesting that rifaximin is efficacious in improving abdominal pain in adults with IBS-D even after repetitive treatment courses. Women with IBS-D had significantly greater abdominal pain response with rifaximin vs placebo, but response did not differ significantly between rifaximin and placebo in men, potentially because of issues related to sample size.

Table 5. Response to treatment for baseline abdominal pain score subgroups[a]

Outcome, n (%)	Baseline abdominal pain score <4.6			Baseline abdominal pain score ≥4.6		
	Rifaximin 550 mg t.i.d. (n = 165)	Placebo (n = 155)	*P* value	Rifaximin 550 mg t.i.d. (n = 163)	Placebo (n = 153)	*P* value
Abdominal pain and stool consistency	58 (35.2)	38 (24.5)	0.04	58 (35.6)	41 (26.8)	0.09
Abdominal pain	89 (53.9)	68 (43.9)	0.07	85 (52.1)	67 (43.8)	0.14
Durable abdominal pain response	42[a] (28.2)	29[b] (20.4)	0.12	46[c] (31.5)	30[d] (21.3)	0.0496

t.i.d., 3 times daily.
[a]Last observation carried forward.
[b]n = 149.
[c]n = 142.
[d]n = 146.
[e]n = 141.

Abdominal pain response was comparable between treatment groups regardless of double-blind baseline abdominal pain intensity (i.e., abdominal pain scores <4.6 or ≥4.6; based on scores measured during the past 2 weeks of the 18-week open-label observation phase). However, a significantly higher percentage of patients with more severe abdominal pain (i.e., a score of ≥4.6) had a durable response with rifaximin vs placebo. Thus, rifaximin appears to be clinically beneficial in patients with more severe symptoms of IBS, which is important given the findings of a survey conducted in 2014 of adults in the United States experiencing gastrointestinal issues (26). The results of this survey indicated that approximately one-third of 1,094 patients diagnosed with IBS-D experienced severe abdominal pain/discomfort (36%) and considered abdominal pain/discomfort a disruptive symptom (32%) (26). Furthermore, Cash et al. (23) showed in the TARGET 3 study, rifaximin improved the IBS QOL questionnaire scores in patients receiving repeat rifaximin treatment compared with placebo. Thus, it is possible that reduction of pain may lead to greater durable symptom reduction and benefits in QOL in patients with more severe abdominal pain compared with those with less severe abdominal pain. However, it is also possible that concurrent psychologic comorbidities (e.g., anxiety and depression) may affect QOL in patients with IBS (27); the potential effect of these comorbidities on the QOL outcomes in TARGET 3 was not examined by Cash et al. (23). Furthermore, it is not known whether the patients included in the current post hoc analysis had long-term improvements in QOL.

The definition of abdominal pain response (i.e., ≥30% improvement from baseline in the mean weekly abdominal pain score) was recommended by the FDA as industry guidance for the design of IBS clinical studies (3). The ≥30% improvement from baseline threshold has been shown to be clinically relevant in chronic pain (28) and IBS (29). However, given that this threshold of abdominal pain response has not been rigorously studied, the FDA also recommended examination of different thresholds for abdominal pain response (3), which was conducted in this analysis. As might be expected, in both the open-label and double-blind responder analyses, the percentage of patients achieving response with rifaximin increased as the threshold and/or duration for abdominal pain response decreased. For patients in the double-blind treatment phase, findings achieved significance using the industry guidance threshold and duration noted above (≥30% improvement from baseline for ≥2 of 4 weeks). Statistical significance was not observed for assessments of ≥40% and higher reductions from baseline in abdominal pain. However, this analysis was not powered to examine various definitions of abdominal pain response, potentially limiting the ability to determine treatment differences because the number of patients in each group decreased with increasing threshold stringency.

A limitation of this analysis includes the post hoc nature of data analysis. Furthermore, patients included in this analysis had to meet the inclusion criteria for participation in TARGET 3, which included rating their average abdominal pain as ≥3 on a scale from 0 (no pain) to 10 (worst possible pain) (21), so the results of this analysis may not be applicable to patients with less severe IBS-D–related abdominal pain. In addition, open-label responders who did not meet the study definition for relapse of IBS-D symptoms (loss of response for either weekly abdominal pain or stool consistency for ≥3 weeks of a consecutive ongoing 4-week period during the 18-week observation phase) were discontinued from the study; thus, 35.6% of open-label responders did not progress to the double-blind treatment phase of the study (21). In conclusion, these data support the efficacy of rifaximin 550 mg t.i.d. for 2 weeks for improving abdominal pain in adults with IBS-D alongside improvement of other symptoms.

CONFLICTS OF INTEREST

Guarantor of the article: Anthony Lembo, MD.

Specific author contributions: A.L. was involved with the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critically revising the manuscript for important intellectual content, and approving the final draft for submission. S.S.C.R. was involved with the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critically revising the manuscript for important intellectual content, and approving the final draft for submission. Z.H. was involved with drafting of the manuscript, critically revising the manuscript for important intellectual content, and approving the final draft for submission. M.P. was involved with the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critically revising the manuscript for important intellectual content, and approving the final draft for submission.

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Potential competing interests: A.L. reports serving as a consultant for Salix Pharmaceuticals. S.S.C.R. reports receiving a research grant for rifaximin in irritable bowel syndrome from Salix Pharmaceuticals. Z.H. reports being an employee of Salix Pharmaceuticals. M.P. reports serving as a consultant for and receiving research grants from Salix Pharmaceuticals. In addition, the Cedars-Sinai Medical Center has a licensing agreement with Salix Pharmaceuticals.

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Study Highlights

WHAT IS KNOWN

- ✓ Abdominal pain is the principal symptom in patients with IBS.
- ✓ Rifaximin is a nonsystemic antibiotic approved for adults with IBS-D.
- ✓ The efficacy of rifaximin for improving abdominal pain in IBS has not been well demonstrated.

WHAT IS NEW HERE

- ✓ Abdominal pain improvement after a 2-week treatment with rifaximin in patients with IBS-D was clinically significant.
- ✓ Abdominal pain response with double-blind repeat rifaximin treatment was durable through 10 weeks post-treatment.

TRANSLATIONAL IMPACT

- ✓ A 2-week course of rifaximin provides clinically significant and durable improvement in abdominal pain, a key symptom in IBS-D.

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