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Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome

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BACKGROUND & AIMS: Few treatments have demonstrated efficacy and safety for diarrhea-predominant irritable bowel syndrome (IBS-D). A phase 3, randomized, double-blind, placebo-controlled trial was performed to evaluate the safety and efficacy of repeat treatment with the nonsystemic antibiotic rifaximin. **METHODS:** The trial included adults with IBS-D, mean abdominal pain and bloating scores of 3 or more, and loose stool, located at 270 centers in the United States and Europe from February 2012 through June 2014. Those responding to a 2-week course of open-label rifaximin 550 mg 3 times daily, who then relapsed during an observation phase (up to 18 weeks), were randomly assigned to groups given repeat treatments of rifaximin 550 mg or placebo 3 times daily for 2 weeks. The primary end point was percentage of responders after first repeat treatment, defined as a decrease in abdominal pain of ≥30% from baseline and a decrease in frequency of loose stools of ≥50% from baseline, for 2 or more weeks during a 4-week post-treatment period. **RESULTS:** Of 1074 patients (44.1%) who responded to open-label rifaximin, 382 (35.6%) did not relapse and 692 (64.4%) did; of these, 636 were randomly assigned to receive repeat treatment with rifaximin (n = 328) or placebo (n = 308). The percentage of responders was significantly greater with rifaximin than placebo (38.1% vs 31.5%; $P = .03$). The percentage of responders for abdominal pain (50.6% vs 42.2%; $P = .018$) was significantly greater with rifaximin than placebo, but not stool consistency (51.8% vs 50.0%; $P = .42$). Significant improvements were also noted for prevention of recurrence, durable response, and bowel movement urgency. Adverse event rates were low and similar between groups. **CONCLUSIONS:** In a phase 3 study of patients with relapsing symptoms of IBS-D, repeat rifaximin treatment was efficacious and well tolerated. ClinicalTrials.gov ID: NCT01543178.

Keywords: Bloating; Functional Bowel Disease; Nonabsorbed; Xifaxan.

Diarrhea-predominant irritable bowel syndrome (IBS-D) is a common gastrointestinal disorder characterized by recurring abdominal pain, bloating, and loose stools in the absence of structural or biochemical abnormalities.[1] Nonpharmacologic options for the treatment of IBS-D include psychological approaches, dietary and lifestyle modifications, probiotics, and fiber supplementation, although each has shown variable and less than optimal relief of IBS-D symptoms.[2–4] Pharmacologic therapies, such as anti-diarrheals (eg, loperamide),[3] have limited beneficial effects on global IBS symptoms (eg, abdominal pain), and the $5HT_3$ antagonist alosetron is approved only for women with severe, treatment-refractory IBS-D,[3] with substantial restrictions on its use. Antidepressants, such as tricyclic agents, although not approved for the treatment of IBS-D, have been considered efficacious for reducing abdominal pain and global IBS symptoms in patients with IBS.[2] However, data on the efficacy of these agents specifically for treatment of IBS-D are limited.[2] Eluxadoline, a twice-daily μ-opioid receptor agonist and δ-opioid receptor antagonist,[5] was approved in 2015 for the treatment of IBS-D.

Patients with IBS have alterations in the intestinal microbiota compared with healthy individuals[6–14]; therefore, the intestinal microbiota may be an effective target for treatment of IBS-D. Rifaximin is an oral, minimally absorbed, broad-spectrum antimicrobial agent that targets the gastrointestinal tract and is associated with a low risk of clinically relevant bacterial antibiotic resistance.[15–18] Rifaximin was approved by the US Food and Drug Administration in May 2015 for the treatment of IBS-D in adults. In 2 large, multicenter, phase 3 trials of patients with IBS-D (Targeted, Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for IBS-D [TARGET] 1 and 2), 40.7% of patients treated with rifaximin 550 mg 3 times daily (TID) for 2 weeks experienced adequate relief of global IBS symptoms for ≥2 of the first 4 weeks post-treatment compared with 31.7% of patients treated with placebo (Δ 9%; $P < .001$, pooled data).[15] In addition, a greater percentage of rifaximin-treated than placebo-treated patients reported durable improvement in IBS-D symptoms for at least 10 weeks post-treatment ($P = .001$, pooled data). However, the persistence of this treatment effect beyond the 10-week follow-up period, assessed in TARGET 1 and 2, and the efficacy and safety of

Abbreviations used in this paper: **AE, adverse event; IBS-D, diarrhea-predominant irritable bowel syndrome; TARGET, targeted, nonsystemic antibiotic rifaximin gut-selective evaluation of treatment for IBS-D; TID, three times daily.**

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repeated treatment after clinical response and subsequent symptom relapse, had only been evaluated in open-label, retrospective studies.[19,20]

The aim of this trial, which included an open-label enrichment phase followed by a randomized, placebo-controlled phase, was to determine the efficacy and safety of repeat treatment with rifaximin in patients with IBS-D who had responded to a 2-week course of rifaximin and subsequently experienced IBS symptom recurrence. Specifically, the primary efficacy assessment compared the percentage of patients who were repeat responders for both abdominal pain and stool consistency during the first 4 weeks after a second course of treatment (repeat treatment with rifaximin or treatment with placebo).

Methods

Study Patients

Eligible patients were 18 years of age or older; had a colonoscopy in the past 10 years or underwent a flexible sigmoidoscopy with biopsies; received a diagnosis of IBS (confirmed by Rome III diagnostic criteria); and did not have adequate relief of global IBS symptoms and bloating during a screening phase. Exclusion criteria included renal or hepatic disease, diabetes, and history of inflammatory bowel disease; previous gastrointestinal surgery; abnormal thyroid function not adequately controlled by thyroid medication; and infection with human immunodeficiency virus or hepatitis B or C.

Based on daily responses to a diary questionnaire (Supplementary Table 1) during the placebo-screening phase, patients must have rated their average abdominal pain $\geq$3 (scale 0–10: 0 = no pain; 10 = worst possible pain) and bloating $\geq$3 (scale 0–6: 0 = not at all; 6 = a very great deal) and have experienced loose stools for $\geq$2 days in a week with a Bristol Stool Scale type 6 (fluffy pieces with ragged edges, a mushy stool) or 7 (watery stool, no solid pieces; entirely liquid stool). These 3 inclusion criteria had to be met for patients to proceed in the study. Furthermore, patients were excluded if (after initiating diary assessments during the placebo-screening phase) they were taking anti-diarrheals, anti-spasmodics, narcotics, prokinetic drugs, warfarin, drugs indicated for IBS (eg, alosetron, lubiprostone), or products marketed as probiotics; patients also were excluded if they were taking rifaximin or any antibiotic within 14 days before providing written informed consent. Patients could continue to take antidepressant agents, provided that they had been taking a stable dose for at least 6 weeks before providing written informed consent. The protocol was approved by all institutional review boards and ethics committees at participating sites, and all patients provided written informed consent. All authors had full access to the study data and reviewed and approved the final manuscript.

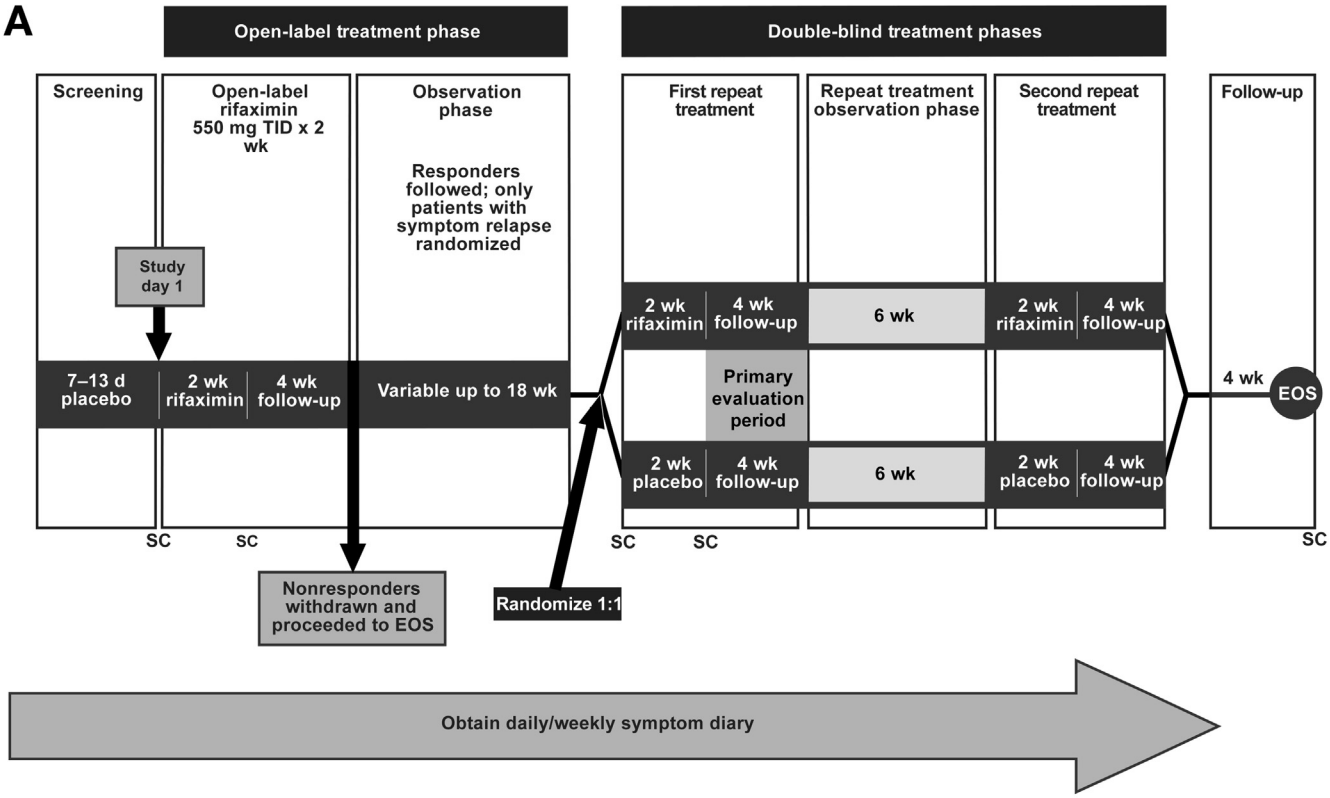
Study Design

In total, 270 centers in the United States, Germany, and the United Kingdom participated in the randomized, double-blind, placebo-controlled, 51-week, phase 3 trial (Figure 1*A*) conducted from February 2012 through June 2014 (ClinicalTrials.gov ID: NCT01543178). After a prescreening eligibility phase, patients entered into a single-blind screening (ie, baseline) phase of placebo TID for 10 $\pm$ 3 days. After completion of the screening phase, patients meeting all eligibility criteria entered into the open-label treatment phase, which consisted of open-label treatment with rifaximin 550 mg TID for 2 weeks, followed by a 4-week assessment period to determine response to rifaximin. A responder was defined as a patient simultaneously meeting weekly response criteria for abdominal pain ($\geq$30% decrease from baseline in mean weekly pain score) and stool consistency ($\geq$50% decrease from baseline in number of days/week with Bristol Stool Scale type 6 or 7 stool) during $\geq$2 of the 4 weeks after treatment. Responders to open-label rifaximin were then monitored in an observation phase for up to an additional 18 weeks or until symptom relapse occurred. Patients who failed to meet the prespecified weekly response criteria for both abdominal pain and stool consistency after the initial open-label rifaximin treatment were classified as nonresponders and withdrawn from the trial.

Patients who were classified as responders to the initial open-label rifaximin treatment and who experienced a relapse in IBS-D symptoms (defined as a loss of treatment response for either weekly abdominal pain [<30% decrease from baseline in mean weekly pain score] or stool consistency [<50% decrease from baseline in number of days/week with Bristol Stool Scale type 6 or 7 stool] for $\geq$3 weeks of a consecutive, rolling 4-week period during the 18-week observation phase) entered into the double-blind treatment phase of the trial, in which patients were randomly assigned (1:1) to receive 2 repeat treatment courses of rifaximin 550 mg TID or placebo TID for 14 days. Randomization was stratified by site. Each site used a randomization code generated and maintained by a clinical research organization by a block randomization schema (block size of 2) using a computerized interactive voice or web response system that was independent of other centers' randomization codes. Response to repeat treatment was assessed during the 4 weeks immediately after a repeat treatment course. The prespecified primary evaluation period for the trial was the 4-week follow-up period after the first repeat treatment. However, all patients, regardless of response or relapse status after the first repeat treatment, received a second repeat treatment with the same treatment assigned at randomization (ie, rifaximin 550 mg or placebo TID for 14 days). The second repeat treatment course was initiated 10 weeks after completion of the first repeat treatment course (ie, after the 4-week primary evaluation period and 6-week repeat treatment observation phase) and was included to assess the safety of additional treatment with rifaximin. The overall trial design reflected input from the United States and European health authorities, and is in keeping with the subsequent publication of US Food and Drug Administration and European Medicines Agency guidance for the development of drugs for IBS.[21–23]

Efficacy End Points and Safety Assessments

An interactive voice or web response system was used to collect responses to daily symptom questions and a separate weekly global IBS symptom question (Supplementary Table 1). The primary end point of the trial was the percentage of patients who were responders (as defined here) for both abdominal pain and stool consistency during the 4-week follow-up after the first repeat treatment course (see Figure 1*A*). Three key secondary end points were evaluated:



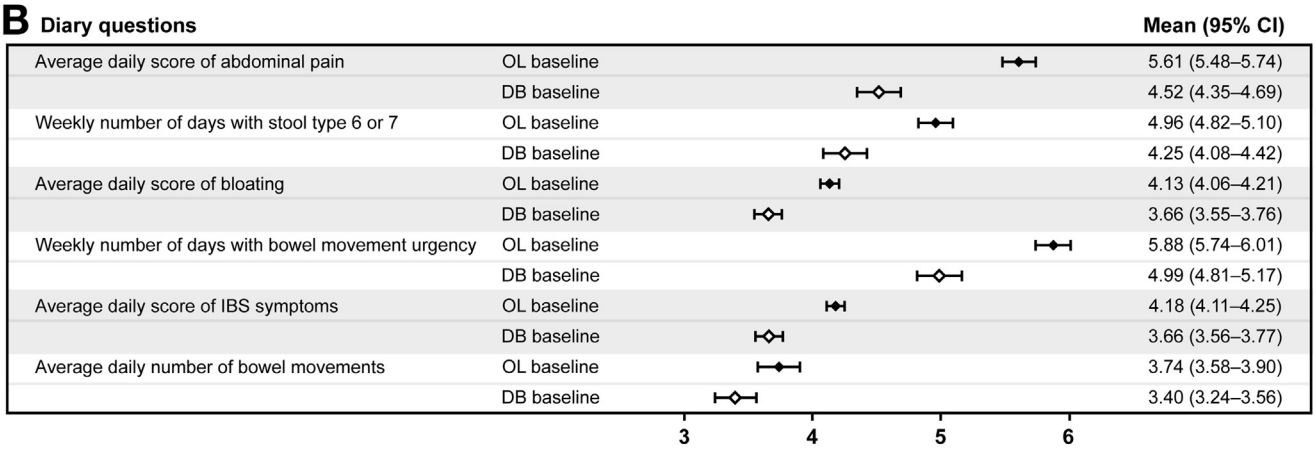


Figure 1. Study design (*A*) and mean baseline IBS symptom severity for patients entering the open-label treatment phase versus the same patients entering the double-blind, first repeat treatment phase (n = 636) (*B*). DB, double-blind; EOS, end of study; IBS, irritable bowel syndrome; OL, open-label; SC, stool sample collection time point.

1. Prevention of recurrence: percentage of responders who did not have recurrence through the end of the 6-week repeat treatment observation phase and continued to respond without recurrence through the end of the second repeat treatment phase;
2. Sustained IBS symptom relief ("durable" response): percentage of responders who did not have recurrence through the 6-week repeat treatment observation phase; and
3. Bloating response: percentage of patients with ≥1-point decrease from baseline in weekly average bloating score for ≥2 weeks during the 4-week primary evaluation period.

Additional efficacy assessments included bowel movement urgency and daily global IBS symptoms (all; Supplementary Table 1). Bowel movement urgency response was defined as ≥30% improvement from baseline in the percentage of days with urgency for ≥2 weeks during the 4-week primary evaluation period. Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, and vital sign measurements. Stool samples were collected before and after open-label rifaximin, before and after the first double-blind repeat treatment, and at study end. In order to receive open-label rifaximin, patients were required to test negative for *Clostridium difficile* toxins A and B via enzyme immunoassay.

Statistical Analyses

Sample size was estimated assuming that 40% and 55% of patients in the placebo and rifaximin groups, respectively (15% treatment difference), would achieve the primary end point criteria (weekly response for abdominal pain and stool consistency during at least 2 of the 4 weeks) during the primary evaluation period with a significance level of 5% ($\alpha = .05$). With these assumptions, a sample size of 300 patients in each treatment group would provide $\geq$90% power to detect statistically significant treatment differences. All analyses were stratified by analysis center.

Missing data were handled using the "worst-case" analysis methodology for the primary end point and key secondary end points. Individual patient responses from daily diary questions were summarized into a weekly value for which at least 4 days of data were recorded within a week; patients who reported <4 days of diary data in a given week were considered nonresponders for that week, regardless of the data collected for that week. The primary analysis using worst-case methodology employed the Cochran–Mantel–Haenszel method, adjusting for analysis center and time to recurrence. A sensitivity analysis using multiple imputation for the primary efficacy end point was also conducted, using the Markov Chain Monte Carlo method, adjusting for analysis center, time to recurrence, and recurrence type. Other efficacy end point analyses were conducted using last observation carried forward. Binary data were analyzed using the Cochran–Mantel–Haenszel method. Durable response was analyzed by the Smirnov test. Time to recurrence was determined by the Kaplan–Meier method and analyzed by log-rank test. Symptom severity reported during the week before entry into the double-blind phase (first repeat treatment phase) was used as the baseline for assessing response to treatment. Change from baseline in continuous outcomes was analyzed using fixed-effects linear models with fixed effects for study arm, analysis center, and baseline value as covariates.

The safety population was the same as the intent-to-treat population. Safety was evaluated for the open-label treatment phase (2-week open-label rifaximin, 4-week follow-up, and up to 18 weeks of observation); while on treatment during the double-blind treatment phase (first 2-week repeat treatment and second 2-week repeat treatment); and overall during the double-blind treatment, observation, and follow-up (entire double-blind treatment phase and final 4-week follow-up phase). Analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Open-label Treatment Phase

Among the 2579 patients with IBS-D who received open-label rifaximin 550 mg TID, 2438 were evaluable for efficacy. Of these patients, 1074 (44.1%) experienced improvement in both abdominal pain and stool consistency on the same weeks for $\geq$2 of 4 weeks after treatment and were considered responders and entered the observation phase (up to 18 weeks; see Supplementary Figure 1). In an individual assessment of these 2 symptom components, 56.8% of the 2438 patients were classified as abdominal pain responders and 60.1% were classified as stool consistency responders. During the observation phase, 692 (64.4%) patients experienced symptom relapse, and 636 of these patients (median time to symptom recurrence, 10.0 weeks) were randomized to double-blind repeat treatment. However, 382 patients (35.6%) did not experience relapse during the 18-week observation phase before being withdrawn from the trial for any reason and did not proceed to double-blind repeat treatment.

The demographics and baseline characteristics of the 636 randomized patients were similar between treatment groups and similar to the overall population entering the initial open-label phase and the population not continuing into the double-blind phase (Table 1). However, baseline symptom scores were significantly lower at the time of randomization than those reported before entering the initial open-label treatment phase ($P < .001$ for all; paired t test) (Figure 1*B*). For example, at the time of randomization, patients were experiencing, on average, a 20% improvement in abdominal pain (ie, less severe abdominal pain) relative to their symptom severity before open-label rifaximin.

Double-Blind Repeat Treatment Phase

Upon repeat treatment, 38.1% of rifaximin-treated patients were primary end point responders, compared with 31.5% of placebo-treated patients using the worst-case analysis for missing data (Δ 7%; $P = .03$; Table 2). A multiple imputation sensitivity analysis for missing data resulted in a similar treatment difference (Δ 8%) with rifaximin (40.2%) vs placebo (32.4%; $P = .01$; 95% confidence interval, 0.4%–15.3%). For the individual components of the primary efficacy end point, a significantly greater percentage of patients retreated with rifaximin vs placebo were responders for abdominal pain (50.6% vs 42.2% with placebo; Δ 9%; $P = .018$), but not stool consistency (51.8% vs 50.0% with placebo; Δ 2%; $P = .42$). For the 3 key secondary end points, a significantly greater percentage of rifaximin-retreated patients were responders for IBS prevention of recurrence and sustained IBS symptom relief (durable response) relative to placebo-treated patients (Table 2). No significant group difference in the percentage of responders for bloating was detected using the worst-case analysis for missing data (Table 2). A greater percentage of rifaximin-treated patients were responders for bowel movement urgency compared with placebo-treated patients (48.5% vs 39.6%, respectively; Δ 9%; $P = .03$ [last observation carried forward]). Mean changes over time for IBS symptoms (ie, abdominal pain, stool consistency, bloating, stool frequency, and bowel movement urgency) improved after the first rifaximin repeat treatment and improved again after the second rifaximin repeat treatment, when compared with placebo (see Figure 2 for abdominal pain and Supplementary Figures 2–6 for other symptoms).

Safety

In patients who entered the repeat treatment phase, AEs were reported in 140 (42.7%) and 140 (45.5%) patients taking rifaximin vs placebo, respectively (Table 3). AEs considered by investigators to be related to study drug were experienced by 6 (1.8%) and 8 (2.6%) patients in the

Table 1. Patient Demographic and Baseline Characteristics at Enrollment[a]

Characteristic	Open-label population		Double-blind population	
	Rifaximin, 550 mg TID (n = 2579)	Non–double-blind population (n = 1943)	Rifaximin, 550 mg TID (n = 328)	Placebo (n = 308)
Age, *y*, mean (SD)	46.4 (13.7)	46.3 (13.5)	47.9 (14.2)	45.6 (13.8)
Sex, n (%)				
Male	819 (31.8)	624 (32.1)	106 (32.3)	89 (28.9)
Female	1760 (68.2)	1319 (67.9)	222 (67.7)	219 (71.1)
Race, n (%)				
White	2155 (83.6)	1620 (83.4)	273 (83.2)	262 (85.1)
Black	289 (11.2)	221 (11.4)	37 (11.3)	31 (10.1)
Other	135 (5.2)	102 (5.2)	18 (5.5)	15 (4.9)
Duration since first onset of IBS symptoms, *y*, mean (SD)	10.9 (10.8)	10.8 (10.8)	11.4 (11.0)	11.2 (10.9)
Average daily scores, mean (SD)				
Abdominal pain	5.5 (1.7)	5.5 (1.7)	5.7 (1.7)	5.5 (1.6)
Stool consistency	5.6 (0.8)	5.6 (0.9)	5.6 (0.8)	5.6 (0.8)
Bloating	4.1 (0.9)	4.1 (0.9)	4.2 (0.9)	4.1 (0.9)
IBS symptoms	4.2 (0.9)	4.1 (0.9)	4.2 (0.9)	4.1 (0.9)
No. of daily bowel movements, mean (SD)	3.9 (2.2)	3.9 (2.2)	3.8 (2.1)	3.7 (2.1)
Days with BSS type 6 or 7 stool in a week, mean (SD)	4.9 (1.8)	4.9 (1.9)	4.9 (1.8)	5.0 (1.7)
Days with bowel movement urgency in a week, mean (SD)	5.9 (1.7)	5.9 (1.7)	5.9 (1.7)	5.8 (1.7)
Country				
United States	2567 (99.5)	1931 (99.4)	328 (100)	308 (100)
United Kingdom	12 (0.5)	12 (0.6)	0	0

BSS, Bristol Stool Scale.
[a]Safety population and intent-to-treat population during double-blind repeat treatment phases were the same.

rifaximin and placebo groups, respectively. Reports of AEs resulting in study discontinuation during the double-blind phases of the study were rare for the 636 patients, occurring in just 1 patient (0.3%) in each treatment group. The most commonly reported AEs occurred with similar frequency in each treatment group (Table 3). Constipation was only reported in 1 (0.3%) patient in the rifaximin group and 3 (1.0%) patients in the placebo group. The profile and incidence of AEs in the double-blind phase was comparable with that reported during the open-label phase. When AEs

Table 2. Primary and Key Secondary End Points

Assessment	Responders, n/total (%)		*P* value (95% CI)
	Rifaximin, 550 mg TID (n = 328)	Placebo (n = 308)	
Primary end point			
Abdominal pain and stool consistency[a,b]	125/328 (38.1)	97/308 (31.5)	.03 (0.9 to 16.9)
Key secondary end points			
Prevention of recurrence[b,c]	39/295 (13.2)	20/283 (7.1)	.007 (2.5 to 20.0)
Durable response[b,d]	56/328 (17.1)	36/308 (11.7)	.04 (1.4 to 16.6)
Bloating[b,e]	153/328 (46.6)	127/308 (41.2)	.14 (−0.9 to 15.0)

[a]Percentage of responders to repeat treatment with rifaximin, defined as improvement in both abdominal pain and stool consistency during ≥2 weeks of the 4-week primary evaluation period (ie, primary end point).
[b]Missing data analyzed using worst-case analysis methodology.
[c]Analysis in population that received a second repeat treatment. Prevention of recurrence was defined as adequate relief in both abdominal pain and stool consistency during the 4-week primary evaluation period, with no recurrence during the 6-week treatment-free repeat treatment observation phase and the second 6-week repeat treatment phase.
[d]Sustained IBS symptom relief (ie, durable response) was defined as adequate relief in both abdominal pain and stool consistency during the 4-week primary evaluation period, with no recurrence through the 6-week treatment-free repeat treatment observation phase.
[e]Percentage of patients with a ≥1-point decrease from baseline in weekly average bloating score for ≥2 weeks during the 4-week primary evaluation period.

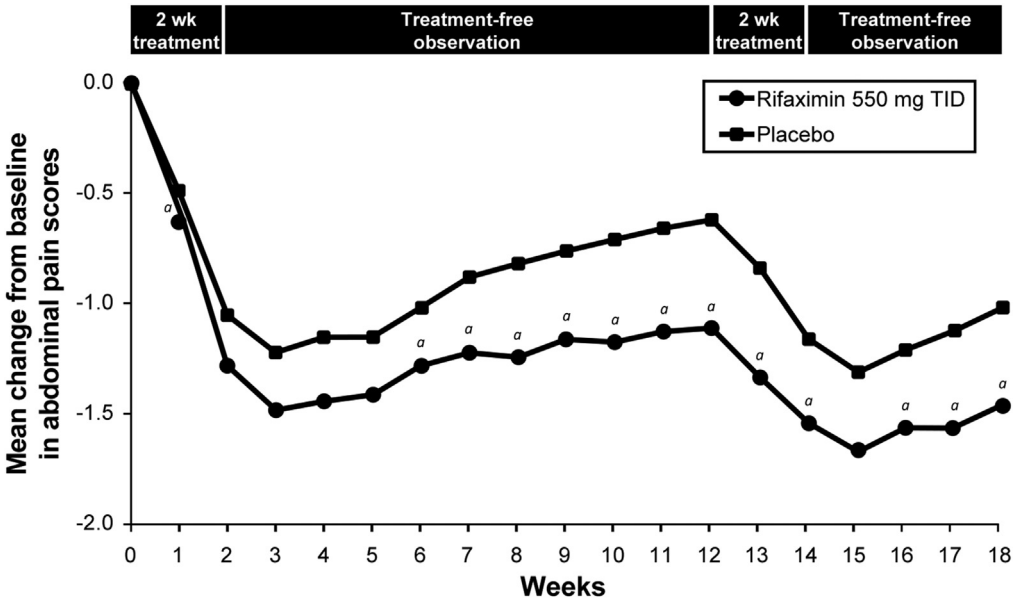


Figure 2. Change from baseline in average daily abdominal pain scores during the first and second repeat treatment double-blind phases. [a]Statistically significant difference vs placebo. Data were analyzed using last observation carried forward methodology.

were assessed only while on treatment during double-blind phase (during first and second 2-week repeat treatments), the most commonly reported AEs for rifaximin vs placebo were increased alanine aminotransferase levels (2.1% vs 1.0%) and nausea (1.8% vs 1.3%) (Supplementary Table 2). During the double-blind phase, serious AEs were reported for 4 patients in each treatment group, and none of these were considered by investigators to be related to treatment. One patient developed *C difficile* colitis infection 37 days after rifaximin repeat treatment. This patient tested negative for *C difficile* toxins A and B at study entry, had a medical history of *C difficile* infection, and had completed a

Table 3. Summary of Adverse Events During Open-label (n = 2579) and Double-blind (n = 636) Phases[a]

	Open-label population	Double-blind population	
AE, n (%)	Rifaximin, 550 mg TID (n = 2579)	Rifaximin 550 mg TID (n = 328)	Placebo (n = 308)
Any AE	822 (31.9)	140 (42.7)	140 (45.5)
Drug-related AE	85 (3.3)	6 (1.8)	8 (2.6)
Serious AE	28 (1.1)	4 (1.2)[b]	4 (1.3)[c]
Most common AEs[d]			
Nausea	52 (2.0)	12 (3.7)	7 (2.3)
Upper respiratory tract infection	41 (1.6)	12 (3.7)	8 (2.6)
Urinary tract infection	35 (1.4)	11 (3.4)	15 (4.9)
Nasopharyngitis	36 (1.4)	10 (3.0)	9 (2.9)
Alanine aminotransferase increased	24 (0.9)	9 (2.7)	4 (1.3)
Blood creatinine phosphokinase increased	31 (1.2)	9 (2.7)	3 (1.0)
Bronchitis	15 (0.6)	9 (2.7)	5 (1.6)
Aspartate aminotransferase increased	24 (0.9)	7 (2.1)	4 (1.3)
Diarrhea	20 (0.8)	7 (2.1)	3 (1.0)
Influenza	33 (1.3)	7 (2.1)	2 (0.6)
Sinusitis	34 (1.3)	7 (2.1)	7 (2.3)
Headache	42 (1.6)	4 (1.2)	9 (2.9)
Arthralgia	17 (0.7)	3 (0.9)	8 (2.6)

[a]During double-blind phase, AEs were assessed during the first 6-week repeat treatment phase, the 6-week treatment-free repeat treatment observation phase, the second 6-week repeat treatment phase, and the final 4-week follow-up phase.
[b]Four patients experienced serious adverse events: fall (n = 1), *Clostridium difficile* colitis (n = 1), dyspnea (n = 1), and breast cancer (n = 1); none of these were considered by investigators to be related to study drug. All events were classified as moderate in intensity.
[c]Four patients experienced serious adverse events: severe cellulitis (n = 1), moderate noncardiac chest pain and severe coronary artery occlusion (n = 1), moderate transient ischemic attack (n = 1), and severe hypertension and severe transient ischemic attack (n = 1); none of these were considered by investigators to be related to study drug.
[d]≥2.0% of patients in either treatment group and ordered by most common AE in double-blind rifaximin group.

10-day course of cefdinir for a urinary tract infection immediately before development of *C difficile* colitis. No events of increased alanine aminotransferase levels during repeat treatment (Supplementary Table 2) were considered by investigators to be related to rifaximin, none of these events were considered to be serious AEs, and none resulted in discontinuation from the study.

Discussion

Previous trials of rifaximin (TARGET 1 and TARGET 2) have demonstrated that a single 2-week course of therapy improves IBS-D symptoms, such as abdominal pain.[15] While retrospective chart reviews suggest that repeat treatment with rifaximin is safe and effective in patients with recurrent symptoms,[19,20] the durability of effect and efficacy and safety of repeat treatment had not been systematically evaluated. In this randomized, controlled trial, rifaximin-treated patients who responded to an initial, open-label, 2-week course of rifaximin and then relapsed during follow-up (up to 18 weeks) were significantly more likely to respond to repeat treatment with rifaximin compared with placebo (38.1% vs 31.5%; $P = .03$). Importantly, 35.6% of patients did not experience IBS-D symptom relapse for up to 18 weeks of follow-up after responding to the initial, open-label course of rifaximin.

Although the percentage of composite primary end point (abdominal pain and stool consistency) responders was significantly higher with repeat treatment with rifaximin vs placebo, an evaluation of the individual end point components found a statistically significant difference for abdominal pain responders, but not stool consistency responders vs placebo. Likewise, unlike the previous phase 3 trials that reported a significantly higher percentage of patients with weekly improvement in bloating (rifaximin [40.2%] vs placebo [30.3%; $P < .001$, pooled data]),[15] there was no statistically significant difference with regard to bloating observed with repeat treatment with rifaximin vs placebo in the current study.

Consistent with previous trials of rifaximin for IBS,[15,24–26] this agent was well tolerated in the current trial, and the number of overall and serious AEs was similar, apart from nausea, in the rifaximin and placebo groups.[18] Furthermore, the incidence of constipation adverse events during treatment with rifaximin was similar to that for placebo, possibly consistent with a lack of effect of rifaximin on gut motility. Importantly, repeat treatment with rifaximin did not result in an increase in the incidence of AEs. One case of clinical *C difficile* infection was reported in the current trial.

Patients with IBS have been shown to have alterations in gut microbiota compared with healthy controls,[6–14] with several of these studies pointing to the possibility of alterations in the small intestinal microbiota. Using quantitative polymerase chain reaction, patients with IBS-D have been shown to have increased numbers of duodenal coliform bacteria.[14] There is growing evidence that gut microbes can influence intestinal motility, epithelial integrity, bile acid metabolism, and the brain–gut axis communication, thus playing an important role in human health and disease.[27,28] Alterations in the gut microbiota may impact one or more of these gastrointestinal tract activities, and potentially result in IBS symptoms.

Rifaximin is a rifamycin derivative with minimal absorption, which may account, in part, for the tolerability profile observed in this and prior studies. In addition to IBS-D, rifaximin is approved by the US Food and Drug Administration for the treatment of traveler's diarrhea and reduction in risk of hepatic encephalopathy recurrence. In 2 large, randomized, double-blind, placebo-controlled trials (TARGET 1 and 2), a single, 2-week course of rifaximin demonstrated efficacy compared with placebo, as assessed during a 4-week treatment-free follow-up period.[15] In addition, in these trials, many rifaximin-treated patients continued to experience benefit for a follow-up period of 10 weeks.

In the current trial, more than one-third of patients who responded to open-label rifaximin did not experience a relapse of IBS-D symptoms when followed for up to 18 weeks after treatment response. Given that the primary aim of the current trial was to assess the effects of repeat treatment with rifaximin, patients who did not experience loss of response to open-label rifaximin during this period were withdrawn from the trial. Therefore, the duration of efficacy after a single course of rifaximin is unknown in this subgroup of patients. An additional limitation of the study is that it can be difficult to detect rare adverse events with clinical trials of this population size. Furthermore, the study was restricted to a maximum of 3 treatment courses of rifaximin. Given that many patients may require long-term (eg, years) management of IBS-D symptoms, the potential risk-to-benefit profile of periodic administration of a nonsystemic antibiotic after 3 treatment courses is unclear.

The design of the current trial has several aspects worthy of discussion. A potential explanation for the relatively small delta ($\sim\Delta$ 7%) observed after repeat treatment with rifaximin or placebo is that patients who had recurrent IBS symptoms after responding to open-label rifaximin reported that the severity of these symptoms was substantially lower than at open-label baseline. The lesser severity of symptoms at the onset of the first double-blind, repeat treatment phase may reduce the statistical power to detect measurable improvement in symptoms due to a "floor effect."[29] Additionally, this floor effect may have theoretically impacted the ability to detect a statistically significant difference in responders for the individual IBS symptoms of abdominal pain and stool consistency that comprised the primary end point. Despite this, repeat treatment with rifaximin provided improvements beyond the continued symptom improvement achieved with the initial open-label treatment. The second repeat treatment with rifaximin or placebo was given to patients 10 weeks after the first repeat treatment, irrespective of recurrence of IBS symptoms, because the primary purpose of the second repeat treatment was to gain additional data on safety and tolerability associated with rifaximin retreatment rather than efficacy. Finally, the definition of *relapse*, which stipulated that patients could experience recurrent symptoms for abdominal pain or stool consistency or both, created a

degree of heterogeneity in the patients who were randomized. Nevertheless, this design is analogous to common clinical practice and provides information relevant for determining when repeat treatment may be appropriate.

There may be concern that a 7% gain over placebo in improvement of abdominal pain and stool consistency (primary end point) does not indicate a substantial clinical impact. One could hypothesize that the current study design may have played at least some role in this observation. Patients who responded to rifaximin with no observed relapse during the 18-week treatment-free follow-up period did not proceed into the randomized, double-blind phase. Thus, only patients with symptom recurrence were treated with rifaximin or placebo as repeat treatment. In essence, the trial indicated that patients with a lower effect with rifaximin (ie, relapse) responded to a repeat course of treatment. Thus, to succeed in TARGET 3, patients had to achieve criteria for response for a composite end point (abdominal pain and stool consistency) with open-label rifaximin; relapse within a set period of time; and achieve criteria for the composite end point again, in a double-blind fashion, when treatment was repeated. Furthermore, as noted previously, symptom severity at double-blind baseline was reduced compared with open-label baseline, indicating a potential residual benefit of rifaximin in patients who experienced relapse after response to an initial open-label course of the drug. Finally, because this is not a primary efficacy trial, it would not be appropriate to calculate a number needed to treat using the data from this study. Pooled analyses of randomized, placebo-controlled trials have reported the number needed to treat of rifaximin to range from 10.2 to 10.6.[30,31]

This prospective, randomized, placebo-controlled trial demonstrates that repeat treatment (up to 3 courses) with rifaximin 550 mg TID for 2 weeks in patients with recurrent IBS-D symptoms confers significant clinical improvement during a treatment-free follow-up period. Although this study had a positive outcome, questions remain about the role of nonsystemic antibiotics in the long term, particularly when patients with IBS-D may require years of symptom management. Further research is needed to better understand the treatment algorithm in patients who may lose responsiveness to rifaximin.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.08.003.

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Conflicts of interest
These authors disclose the following: Anthony Lembo is a consultant for Salix Pharmaceuticals. Mark Pimentel is a consultant for and has received research grants from Salix Pharmaceuticals. He would also like to report that Cedars-Sinai Medical Center has a licensing agreement with Salix Pharmaceuticals. Satish S. Rao has received a research grant for rifaximin in irritable bowel syndrome from Salix Pharmaceuticals. Philip Schoenfeld is consultant for and has served on the speakers' bureau for Salix Pharmaceuticals; he also is a partner in MD-Evidence, LLC, a medical education and consulting company. Brooks Cash is a consultant for and has served on the speakers' bureau for Salix Pharmaceuticals. Leonard B. Weinstock has served on the speakers' bureau for Salix Pharmaceuticals and also is a primary investigator on a rifaximin trial for irritable bowel syndrome for Salix Pharmaceuticals. Craig Paterson is a former employee of Salix Pharmaceuticals. Enoch Bortey is a former employee of Salix Pharmaceuticals. William P. Forbes is a former employee of Salix Pharmaceuticals.

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