ORIGINAL ARTICLE

Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation

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ABSTRACT

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BACKGROUND

Evidence suggests that gut flora may play an important role in the pathophysiology of the irritable bowel syndrome (IBS). We evaluated rifaximin, a minimally absorbed antibiotic, as treatment for IBS.

METHODS

In two identically designed, phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2), patients who had IBS without constipation were randomly assigned to either rifaximin at a dose of 550 mg or placebo, three times daily for 2 weeks, and were followed for an additional 10 weeks. The primary end point, the proportion of patients who had adequate relief of global IBS symptoms, and the key secondary end point, the proportion of patients who had adequate relief of IBS-related bloating, were assessed weekly. Adequate relief was defined as self-reported relief of symptoms for at least 2 of the first 4 weeks after treatment. Other secondary end points included the percentage of patients who had a response to treatment as assessed by daily self-ratings of global IBS symptoms and individual symptoms of bloating, abdominal pain, and stool consistency during the 4 weeks after treatment and during the entire 3 months of the study.

RESULTS

Significantly more patients in the rifaximin group than in the placebo group had adequate relief of global IBS symptoms during the first 4 weeks after treatment (40.8% vs. 31.2%, P=0.01, in TARGET 1; 40.6% vs. 32.2%, P=0.03, in TARGET 2; 40.7% vs. 31.7%, P<0.001, in the two studies combined). Similarly, more patients in the rifaximin group than in the placebo group had adequate relief of bloating (39.5% vs. 28.7%, P=0.005, in TARGET 1; 41.0% vs. 31.9%, P=0.02, in TARGET 2; 40.2% vs. 30.3%, P<0.001, in the two studies combined). In addition, significantly more patients in the rifaximin group had a response to treatment as assessed by daily ratings of IBS symptoms, bloating, abdominal pain, and stool consistency. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of IBS symptoms, bloating, abdominal pain, and loose or watery stools. (Funded by Salix Pharmaceuticals; ClinicalTrials.gov numbers, NCT00731679 and NCT00724126.)

The irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurring symptoms of abdominal pain, bloating, and altered bowel function in the absence of structural, inflammatory, or biochemical abnormalities.[1] IBS often does not respond to current treatment options, including dietary and lifestyle modifications, fiber supplementation, psychological therapy, and pharmacotherapy.[2,3] Because no reliable biologic or structural markers have been identified, the effects of pharmacotherapy are typically assessed by asking patients to report whether they had adequate relief of IBS symptoms (with a binary response of yes or no).[4] Given the limitations of available therapies, there is an unmet medical need for novel therapeutic approaches.

Patients with IBS may have alterations in the intestinal microbiota,[5-7] thus leading investigators to consider targeting the intestinal microbiota for the treatment of this condition. Although some patients have had improvement with neomycin therapy, clinical trials have shown that it has marginal efficacy, and side effects limit the use of the drug.[8] The use of systemic antibiotics has been reported with mixed results.[9]

Rifaximin (Xifaxan, Salix Pharmaceuticals) is an oral, nonsystemic, broad-spectrum antibiotic that targets the gut and is associated with a low risk of bacterial resistance.[10-12] It has shown efficacy in small-scale studies of IBS.[13,14] We present the results of two large-scale, identically designed, multicenter trials — TARGET 1 and TARGET 2 — of 3 months' duration that examined the relief of IBS symptoms after a 2-week course of rifaximin.

METHODS

STUDY PATIENTS

Eligible patients were at least 18 years of age; had undergone a colonoscopic examination within the previous 2 years; had received a diagnosis of and had current symptoms of IBS (as assessed according to the Rome II diagnostic criteria for IBS[15]), in particular, symptoms of abdominal pain and discomfort; and did not have adequate relief of global IBS symptoms and of IBS-related bloating at both the time of screening and the time of randomization. Eligible patients rated the average daily amount of abdominal pain and of bloating as a score of 2 to 4.5 on a 7-point Likert scoring system (with 0 indicating not at all; 1, hardly; 2, somewhat; 3, moderately; 4, a good deal; 5, a great deal; and 6, a very great deal) and rated the average daily consistency of their stools as 3.5 or more on a 5-point scale for stool consistency (with 1 indicating very hard; 2, hard; 3, formed; 4, loose; and 5, watery) over the course of at least 7 days.

Exclusion criteria were constipation-predominant IBS (according to the definition in the Rome II criteria[15]), a history of inflammatory bowel disease, diabetes, unstable thyroid disease, previous abdominal surgery (other than cholecystectomy or appendectomy), human immunodeficiency virus infection, and renal or hepatic disease. Patients were excluded if they were currently taking alosetron, tegaserod, lubiprostone, warfarin, or antipsychotic, antispasmodic, antidiarrheal, probiotic, or narcotic drugs or if they had taken antibiotics within the previous 14 days or rifaximin within 60 days before signing the informed-consent form for the study. Patients were allowed to take antidepressant agents of the selective serotonin-reuptake inhibitor and tricyclic antidepressant classes, provided that they had been taking a stable dose for at least 6 weeks. All patients provided written informed consent before study-related procedures were initiated.
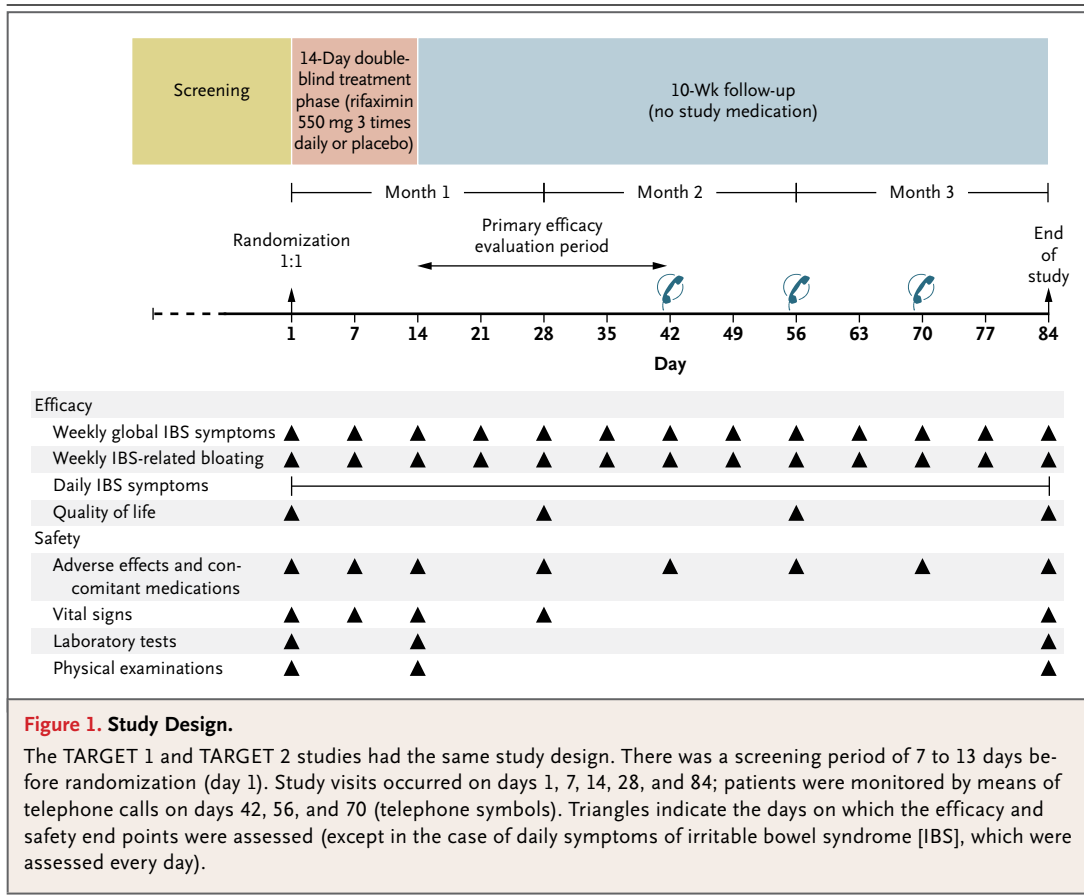
STUDY DESIGN AND PROCEDURES

The protocols were approved by the institutional review board or independent ethics committee at each center, and the studies were conducted in accordance with applicable laws and regulations (see the Supplementary Appendix, available with the full text of this article at NEJM.org). After a screening phase of 7 to 13 days, eligible patients were randomly assigned with the use of an interactive voice-response system to either rifaximin or placebo, in a 1:1 ratio. The randomization code was computer-generated, and randomization was performed in blocks of four, stratified according to center. After completing the 14-day study-treatment period, patients were evaluated for 10 additional weeks. Study visits were conducted on days 1, 7, 14, 28, and 84, and patients were monitored by means of telephone calls on days 42, 56, and 70. Efficacy assessments were obtained daily by means of an interactive voice-response system over the course of the entire study (Fig. 1).

The protocol was designed by Salix Pharmaceuticals in collaboration with the academic au-

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Figure 1. Study Design.

The TARGET 1 and TARGET 2 studies had the same study design. There was a screening period of 7 to 13 days before randomization (day 1). Study visits occurred on days 1, 7, 14, 28, and 84; patients were monitored by means of telephone calls on days 42, 56, and 70 (telephone symbols). Triangles indicate the days on which the efficacy and safety end points were assessed (except in the case of daily symptoms of irritable bowel syndrome [IBS], which were assessed every day).

thors. Data were collected by investigators at each center (see the Supplementary Appendix) and were monitored by Quintiles (a contract research organization) under the supervision of Salix Pharmaceuticals. The data were analyzed by personnel at Salix Pharmaceuticals, in collaboration with the academic authors. All the authors participated in the interpretation of the data and in the writing of the manuscript. The first two authors wrote the first draft of the manuscript, and all the authors, in addition to an employee of Salix, assisted in the revision of subsequent drafts. All the authors made the decision to submit the manuscript for publication. The trial protocol, including the statistical analysis plan, is available at NEJM.org. All the authors vouch for the completeness and veracity of the data and analyses, as well as the fidelity of this report to the trial protocol.

EFFICACY AND SAFETY END POINTS

The primary end point was the proportion of patients who had adequate relief of global IBS symptoms for at least 2 of the 4 weeks during the primary evaluation period (weeks 3 through 6). This end point was determined from the response (yes or no) to the following question, which was asked weekly: "In regard to all your symptoms of IBS, as compared with the way you felt before you started the study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms?" The threshold for clinical relevance — adequate relief during at least 2 weeks per month — was defined prospectively. In addition, the proportion of patients who reported that they had adequate relief during at least 2 weeks per month ("monthly response") during months 1, 2, and 3 was assessed to identify the onset and duration of the therapeutic effect. Patients who started to take antibiotics (other than the study medication) or who took more than two doses of a medication that was prohibited per the study protocol were considered not to have had a response to treatment starting from the time the medication was initiated, regardless of their response data.

The key secondary end point, the proportion of patients who had adequate relief of IBS-related bloating during the primary evaluation period, was determined from the response (yes or no) to the weekly question, "In regard to your symptoms of bloating, as compared with the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptom of bloating?" The onset and duration of relief of bloating were also assessed in an analysis of monthly response, as described above for the primary end point.

For other secondary end points, the proportion of patients who had relief was determined from the patients' daily assessments of IBS symptoms, bloating, and abdominal pain and discomfort (as rated on a 7-point scale); relief was defined as a score of either 0 (not at all) or 1 (hardly) for at least 50% of the days in a given week or a score of 0 (not at all), 1 (hardly), or 2 (somewhat) for 100% of the days in a given week for at least 2 of the 4 weeks during a given month.

An exploratory end point, which was included at the request of the Food and Drug Administration (FDA), was the proportion of patients who had relief of the composite of abdominal pain and discomfort and loose or watery stools (as measured by improvement in stool consistency), on the basis of daily assessments. Relief was defined as a decrease of at least 30% from baseline in weekly mean ratings of IBS-related abdominal pain or discomfort and a weekly mean stool-consistency score of less than 4 (with 4 indicating loose stools and lower scores indicating more formed stools) for at least 2 of the 4 weeks during a given month. This exploratory end point is consistent with the recommended composite end point for IBS with diarrhea in a recently released draft of FDA guidelines.[16] Safety assessments included the monitoring of adverse events, results of clinical laboratory testing, findings from physical examinations, and vital signs.

STATISTICAL ANALYSIS

We estimated the sample size for each study assuming that 40% of the patients in the placebo group and 55% in the rifaximin group would meet the criteria for the primary end point (i.e., would have adequate relief of global IBS symptoms, as assessed weekly) for at least 2 of the first 4 weeks after treatment. With these assumptions, a sample of 300 patients would be needed in each group for the studies to have 95% power to show the 15-percentage-point difference between the groups, at a significance level of 0.05.

All efficacy and safety analyses were performed on a modified intention-to-treat population, which included all patients who received at least one dose of the study drug. Missing data were imputed with the use of the last-observation-carried-forward method, whereby missing values were replaced with the last nonmissing value; baseline values were not carried forward. Two sensitivity analyses were conducted, one in which missing data were regarded as indicating that the patients who terminated the study prematurely had had no relief of symptoms, and the other in which missing data were imputed with the use of the multiple-imputation method.

Binary data (i.e., data on the proportion of patients who had or did not have adequate relief of symptoms) were analyzed with the use of logistic regression; fixed-effect terms included the study group and the analysis center. There were five analysis centers, which we formed prospectively by grouping the study centers according to geographic region in order to assess the effects of geographic location on the end points. For the analysis of ordinal data (i.e., data on the number of months in which patients had relief for at least 2 weeks per month), we used the proportional-odds model for the ordinal outcome. The number of consecutive months with relief during the first 3 months after treatment was summed for each patient, so that each patient received a score of 0, 1, 2, or 3.

We analyzed the changes from baseline in continuous outcomes (i.e., symptom scores) by fitting fixed-effects linear models to the data. An initial model with terms for treatment, analysis center, baseline ratings of the response variable, and interaction of baseline ratings with treatment was fitted. The interaction term was tested at the 0.05 level. A nonsignificant interaction was dropped from the model in subsequent analyses.

Spearman correlation analyses were applied to the mean change from baseline in daily assessments of adequate relief of IBS symptoms (yes or no) to determine whether the weekly assessments of adequate relief paralleled the pattern seen with the daily assessments. Safety data were summarized with the use of descriptive statistics.
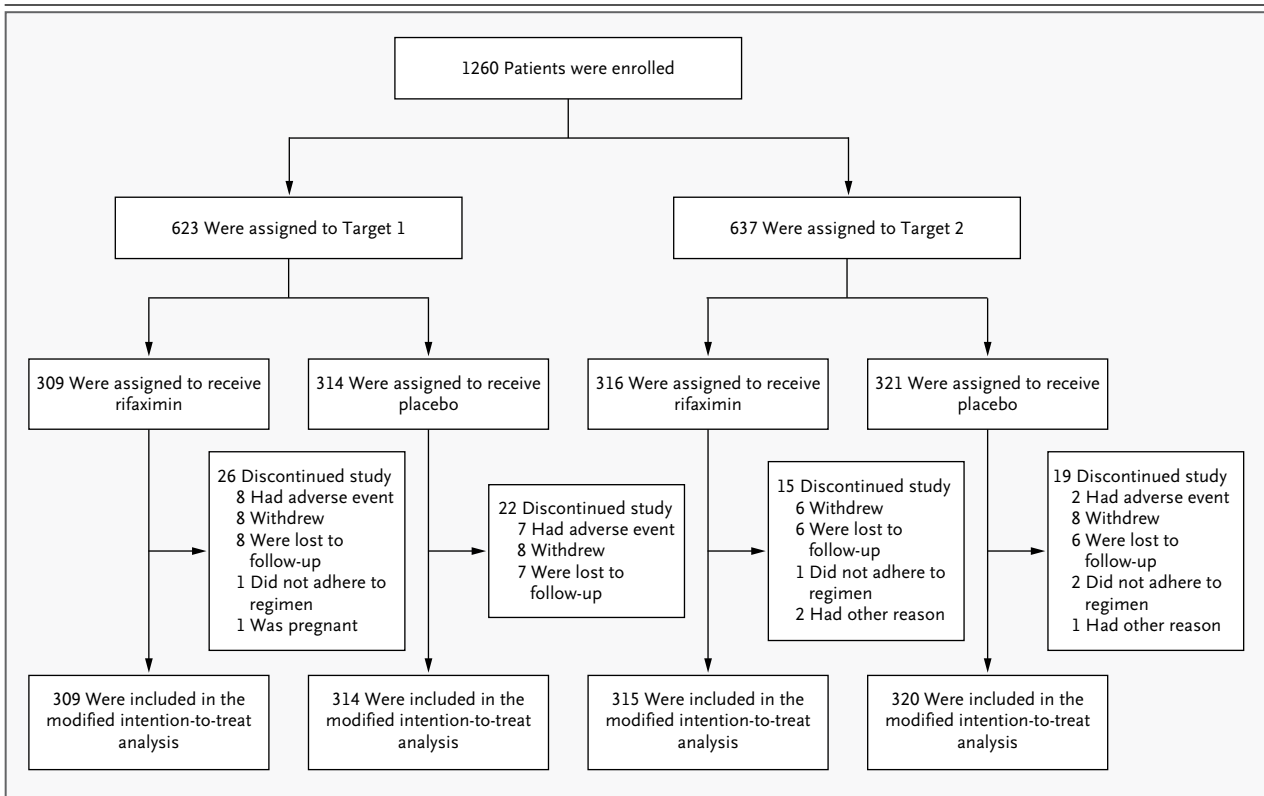
Figure 2. Enrollment, Randomization, and Follow-up in the TARGET 1 and TARGET 2 Studies.

A total of 92.3% of the patients in TARGET 1 and 94.7% of the patients in TARGET 2 completed the study. Two patients from TARGET 2, one in each study group, were excluded from the analysis because they did not take the study drug. Thus, 1258 patients in TARGET 2 received at least one dose of the study drug and were included in the modified intention-to-treat analysis.

RESULTS

STUDY PATIENTS

A total of 1260 patients who had IBS without constipation were enrolled in the studies (623 patients in TARGET 1 and 637 in TARGET 2) and underwent randomization at one of 179 investigative sites in the United States (1217 patients) and Canada (43 patients) (Fig. 2). The studies were conducted in parallel from June 2008 through August 2009. In TARGET 1, all the patients who underwent randomization took at least one dose of the study drug. In TARGET 2, two patients (one in each group) underwent randomization but did not receive a study drug. Thus, 1258 patients received at least one dose of the study drug and were included in the modified intention-to-treat population. More than 90% of the patients completed the entire 12-week study. The baseline characteristics of the patients were similar in the two studies and across treatment groups (Table 1). The rate of adherence to the study drug, defined as the use of at least 70% of the dispensed tablets, was at least 97% in both study groups in both studies.

EFFICACY DURING THE PRIMARY EVALUATION PERIOD (WEEKS 3 THROUGH 6)

Adequate Relief of Global IBS Symptoms

Significantly more patients in the rifaximin group than in the placebo group met the criteria for the primary end point of adequate relief of global IBS symptoms for at least 2 of the first 4 weeks after treatment (40.8% vs. 31.2%, P=0.01, in TARGET 1; 40.6% vs. 32.2%, P=0.03, in TARGET 2; 40.7% vs. 31.7%, P<0.001, in the two studies combined) (Fig. 3A). The last-observation-carried-forward method was applied in the case of 5.8% of the patients in the rifaximin group and 5.7% of the patients in the placebo group in TARGET 1 and in the case of 5.4% in the rifaximin group and 8.4% in the placebo group in TARGET 2. Overall,

Table 1. Demographic and Baseline Characteristics of the Modified Intention-to-Treat Population in the Two Studies.*

Characteristic	TARGET 1			TARGET 2		
	Rifaximin (N=309)	Placebo (N=314)	P Value†	Rifaximin (N=315)	Placebo (N=320)	P Value†
Age — yr	46.2±15.0	45.5±14.6	0.55	45.9±13.9	46.3±14.6	0.72
Age group — no. (%)			0.71			0.44
<65 yr	275 (89.0)	276 (87.9)		285 (90.5)	283 (88.4)	
≥65 yr	34 (11.0)	38 (12.1)		30 (9.5)	37 (11.6)	
Sex — no. (%)			0.15			0.66
Male	74 (23.9)	92 (29.3)		88 (27.9)	95 (29.7)	
Female	235 (76.1)	222 (70.7)		227 (72.1)	225 (70.3)	
Race — no. (%)‡			0.50			0.08
Black or of African ancestry	24 (7.8)	30 (9.6)		21 (6.7)	14 (4.4)	
White	281 (90.9)	280 (89.2)		282 (89.5)	302 (94.4)	
Other	4 (1.3)	4 (1.3)		12 (3.8)	4 (1.2)	
Average daily scores						
Global IBS symptoms§	3.4±0.7	3.4±0.7	0.47	3.4±0.7	3.4±0.7	0.53
IBS-related bloating§	3.3±0.8	3.3±0.7	0.43	3.2±0.7	3.3±0.7	0.28
Abdominal pain and discomfort§	3.3±0.7	3.2±0.7	0.75	3.3±0.7	3.3±0.7	0.69
Stool consistency¶	3.9±0.3	3.9±0.3	0.18	3.9±0.3	3.9±0.3	0.80
Average daily bowel movements — no.	2.9±1.3	3.0±1.4	0.27	3.0±1.6	3.0±1.5	0.78
Days with stool urgency — %‖	81.8±22.3	82.9±22.3	0.53	81.3±22.8	82.2±22.5	0.64
Duration of IBS symptoms — yr**	11.9±10.5	11.4±11.9	0.61	10.8±10.2	11.8±10.4	0.19

* Plus–minus values are means ±SD. IBS denotes irritable bowel syndrome.
† P values were calculated with the use of a t-test for continuous variables and Fisher's exact test for nominal variables.
‡ Race was self-reported.
§ Patients were asked to rate how bothersome their symptoms were on that day, on a scale of 0 to 6. A score of 0 indicated not at all; 1, hardly; 2, somewhat; 3, moderately; 4, a good deal; 5, a great deal; and 6, a very great deal.
¶ Patients were asked to rate the overall stool form of their bowel movements on that day. A score of 1 indicated very hard; 2, hard; 3, formed; 4, loose; and 5, watery.
‖ The percentage of days with stool urgency was calculated with the use of the following formula: 100 × (no. of days with a sense of urgency with any of the bowel movements ÷ no. of days with bowel movements).
** The duration of IBS symptoms was calculated with the use of the following formula: (date written informed consent was provided – date of first IBS symptom) ÷ 365.25.

sensitivity analyses that were performed to address the effect of missing values yielded results that were consistent with those of the primary efficacy analysis (see the Supplementary Appendix). On the basis of daily assessments of IBS symptoms, the proportion of patients with a response to treatment, as rated on a 7-point scale during the primary evaluation period, was significantly greater in the rifaximin group than in the placebo group (42.7% vs. 30.6%, P<0.001, in TARGET 1; 37.8% vs. 28.4%, P=0.007, in TARGET 2; 40.2% vs. 29.5%, P<0.001, in the two studies combined) (Fig. 3A).

Adequate Relief of IBS-Related Bloating

Significantly more patients in the rifaximin group than in the placebo group met the criteria for the key secondary end point, adequate relief of IBS-related bloating for at least 2 of the first 4 weeks after treatment (39.5% vs. 28.7%, P=0.005, in TARGET 1; 41.0% vs. 31.9%, P=0.02, in TARGET 2; 40.2% vs. 30.3%, P<0.001, in the two studies combined) (Fig. 3A). Sensitivity analyses that were performed to assess the effect of missing values yielded similar results (see the Supplementary Appendix). On the basis of daily assessments of IBS-related bloating as rated on a 7-point scale during
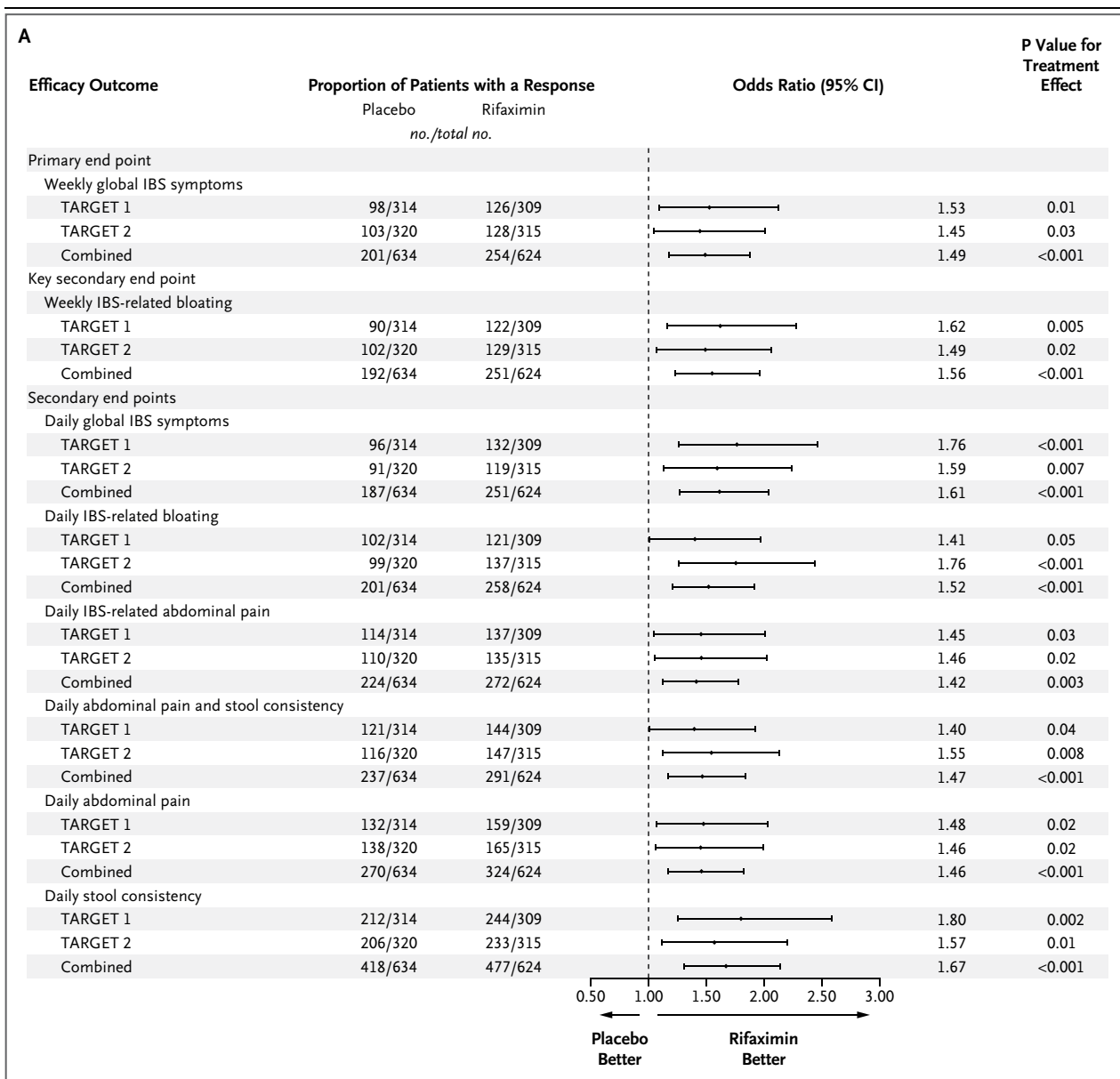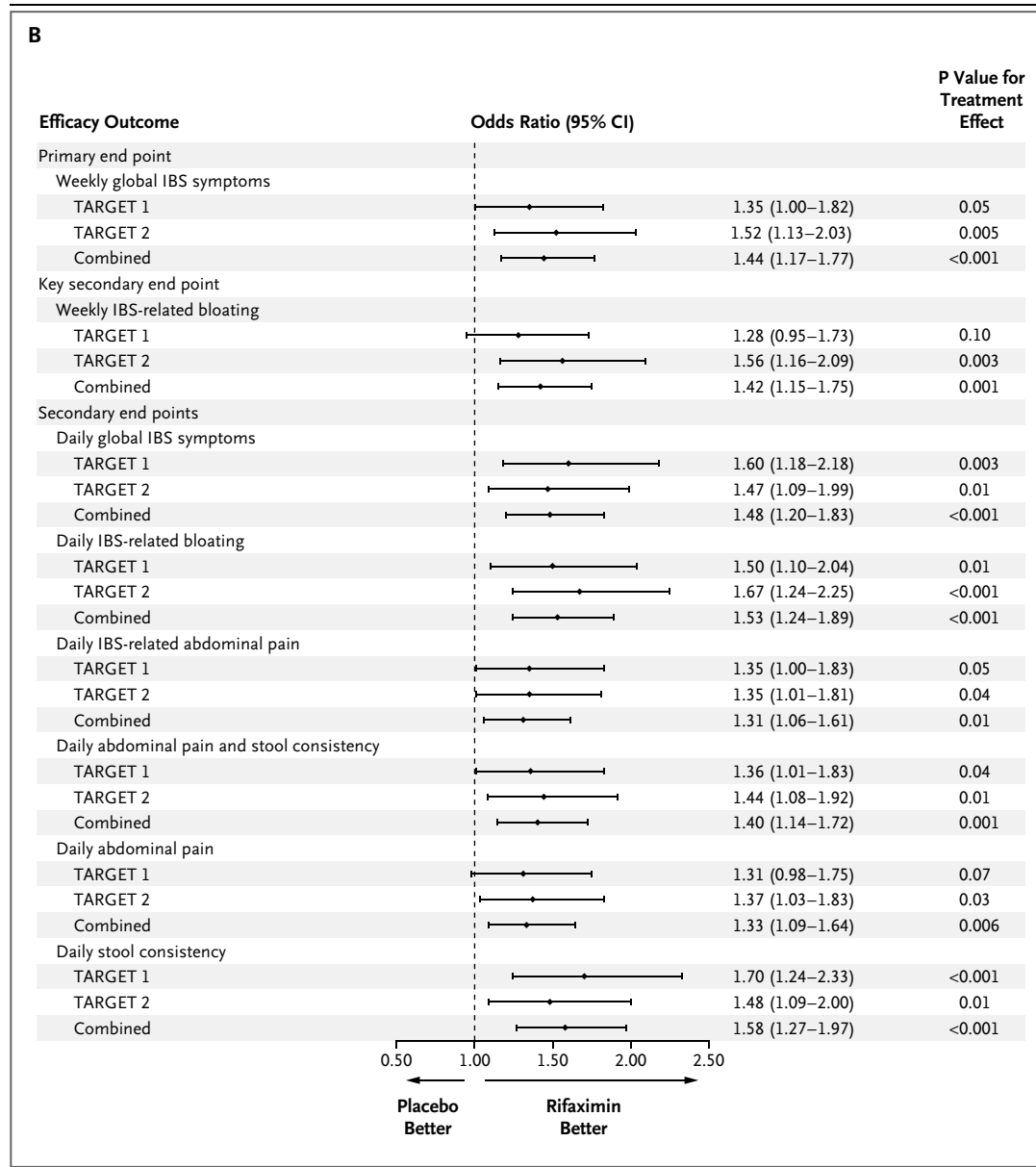
A

Efficacy Outcome	Proportion of Patients with a Response		Odds Ratio (95% CI)		P Value for Treatment Effect
	Placebo	Rifaximin			
	no./total no.				
Primary end point					
Weekly global IBS symptoms					
TARGET 1	98/314	126/309		1.53	0.01
TARGET 2	103/320	128/315		1.45	0.03
Combined	201/634	254/624		1.49	<0.001
Key secondary end point					
Weekly IBS-related bloating					
TARGET 1	90/314	122/309		1.62	0.005
TARGET 2	102/320	129/315		1.49	0.02
Combined	192/634	251/624		1.56	<0.001
Secondary end points					
Daily global IBS symptoms					
TARGET 1	96/314	132/309		1.76	<0.001
TARGET 2	91/320	119/315		1.59	0.007
Combined	187/634	251/624		1.61	<0.001
Daily IBS-related bloating					
TARGET 1	102/314	121/309		1.41	0.05
TARGET 2	99/320	137/315		1.76	<0.001
Combined	201/634	258/624		1.52	<0.001
Daily IBS-related abdominal pain					
TARGET 1	114/314	137/309		1.45	0.03
TARGET 2	110/320	135/315		1.46	0.02
Combined	224/634	272/624		1.42	0.003
Daily abdominal pain and stool consistency					
TARGET 1	121/314	144/309		1.40	0.04
TARGET 2	116/320	147/315		1.55	0.008
Combined	237/634	291/624		1.47	<0.001
Daily abdominal pain					
TARGET 1	132/314	159/309		1.48	0.02
TARGET 2	138/320	165/315		1.46	0.02
Combined	270/634	324/624		1.46	<0.001
Daily stool consistency					
TARGET 1	212/314	244/309		1.80	0.002
TARGET 2	206/320	233/315		1.57	0.01
Combined	418/634	477/624		1.67	<0.001

0.50 1.00 1.50 2.00 2.50 3.00

← Placebo Better   Rifaximin Better →

Figure 3. Analyses of Primary, Key Secondary, and Other Secondary End Points.

The odds ratios for relief of symptoms during the primary evaluation period (weeks 3 through 6 of the study) (Panel A) and for the entire 3-month study period (Panel B) are shown for the modified intention-to-treat population (with the use of the last-observation-carried-forward approach). Two patients from TARGET 2, one in each study group, were excluded from the analysis because they did not take the study drug. The analyses were performed on data from weekly or daily assessments of symptoms, as noted. The analyses of the composite end point of abdominal pain and stool consistency and of the two components of that composite end point were exploratory end points requested by the Food and Drug Administration.

the same primary evaluation period, a significantly greater proportion of patients in the rifaximin group than in the placebo group had relief (39.2% vs. 32.5%, P=0.05, in TARGET 1; 43.5% vs. 30.9%, P<0.001, in TARGET 2; 41.3% vs. 31.7%, P<0.001, in the two studies combined) (Fig. 3A).

Relief of IBS-Related Abdominal Pain and Loose or Watery Stools

A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of IBS-related abdominal pain and discomfort during the primary evaluation period

B

Efficacy Outcome	Odds Ratio (95% CI)		P Value for Treatment Effect
Primary end point			
Weekly global IBS symptoms			
TARGET 1		1.35 (1.00–1.82)	0.05
TARGET 2		1.52 (1.13–2.03)	0.005
Combined		1.44 (1.17–1.77)	<0.001
Key secondary end point			
Weekly IBS-related bloating			
TARGET 1		1.28 (0.95–1.73)	0.10
TARGET 2		1.56 (1.16–2.09)	0.003
Combined		1.42 (1.15–1.75)	0.001
Secondary end points			
Daily global IBS symptoms			
TARGET 1		1.60 (1.18–2.18)	0.003
TARGET 2		1.47 (1.09–1.99)	0.01
Combined		1.48 (1.20–1.83)	<0.001
Daily IBS-related bloating			
TARGET 1		1.50 (1.10–2.04)	0.01
TARGET 2		1.67 (1.24–2.25)	<0.001
Combined		1.53 (1.24–1.89)	<0.001
Daily IBS-related abdominal pain			
TARGET 1		1.35 (1.00–1.83)	0.05
TARGET 2		1.35 (1.01–1.81)	0.04
Combined		1.31 (1.06–1.61)	0.01
Daily abdominal pain and stool consistency			
TARGET 1		1.36 (1.01–1.83)	0.04
TARGET 2		1.44 (1.08–1.92)	0.01
Combined		1.40 (1.14–1.72)	0.001
Daily abdominal pain			
TARGET 1		1.31 (0.98–1.75)	0.07
TARGET 2		1.37 (1.03–1.83)	0.03
Combined		1.33 (1.09–1.64)	0.006
Daily stool consistency			
TARGET 1		1.70 (1.24–2.33)	<0.001
TARGET 2		1.48 (1.09–2.00)	0.01
Combined		1.58 (1.27–1.97)	<0.001

0.50   1.00   1.50   2.00   2.50

Placebo Better ← → Rifaximin Better

(44.3% vs. 36.3%, P=0.03, in TARGET 1; 42.9% vs. 34.4%, P=0.02, in TARGET 2) (Fig. 3A). In an assessment of the composite end point of abdominal pain or discomfort and loose or watery stools, significantly more patients in the rifaximin group than in the placebo group had relief during the primary evaluation period (46.6% vs. 38.5%, P=0.04, in TARGET 1; 46.7% vs. 36.3%, P=0.008, in TARGET 2), and a significantly greater proportion of patients in the rifaximin group had relief with respect to the individual components of this end point (Fig. 3A).

EFFICACY DURING THE ENTIRE STUDY PERIOD (MONTHS 1 THROUGH 3)

Durability of Response on the Basis of Weekly Assessment

In analyses of the monthly response evaluated on the basis of weekly assessments, more patients in the rifaximin group than in the placebo group in both studies had adequate relief of global IBS symptoms within the first month, with continued relief during the first 2 months and during all 3 months in both studies (P=0.05 in TARGET 1, P=0.005 in TARGET 2, and P<0.001 in the two

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Figure 4. Percentage of Patients with Adequate Relief of Global IBS Symptoms in the TARGET 1 and TARGET 2 Studies Combined.

Adequate relief was defined as self-reported relief from symptoms for at least 1 week of every 2-week period. The P value was calculated on the basis of a longitudinal data analysis with the use of a generalized-estimating-equation model, with fixed effects of treatment, analysis center, and week. Similar figures for the individual TARGET 1 and TARGET 2 trials are shown in the Supplementary Appendix.

studies combined, for relief during all 3 months) (Fig. 3B). With respect to IBS-related bloating, in TARGET 1, significantly more patients in the rifaximin group than in the placebo group had adequate relief in the first month, with continued relief during the first 2 months, but there were no significant between-group differences with respect to relief during all 3 months; in TARGET 2, significant benefits of rifaximin were seen with respect to IBS-related bloating for all 3 months (P=0.10 in TARGET 1, P=0.003 in TARGET 2, and P=0.001 in the two studies combined, for relief during all 3 months) (Fig. 3B). The percentages of patients in each group with adequate relief of global IBS symptoms in TARGET 1 and TARGET 2 are provided in Figure 4, and in Figure 1A and 1B in the Supplementary Appendix.

Durability of Response on the Basis of Daily Assessment
The analyses of monthly response evaluated on the basis of daily assessments also support a durable response to rifaximin in patients with IBS over the course of 3 months. Patients treated with rifaximin, as compared with patients who received placebo, had adequate relief of global IBS symptoms during the entire 3 months of the study (P=0.003 in TARGET 1, P=0.01 in TARGET 2, and P<0.001 in the two studies combined) and of IBS-related bloating (P=0.01 in TARGET 1,

P<0.001 in TARGET 2, and P<0.001 in the two studies combined) (Fig. 3B).

An analysis of the monthly response evaluated on the basis of daily assessments of IBS-related abdominal pain and discomfort showed that significantly more patients in the rifaximin group than in the placebo group had relief for the entire 3 months (P=0.05 in TARGET 1, P=0.04 in TARGET 2, and P=0.01 in the two studies combined) (Fig. 3B). An analysis of the monthly response evaluated on the basis of the assessment of the composite end point of abdominal pain and stool consistency also showed a significant benefit with rifaximin as compared with placebo (P=0.04 in TARGET 1, P=0.01 in TARGET 2, and P=0.001 in the two studies combined) (Fig. 3B).

The mean improvement from baseline in daily symptom scores (global IBS symptoms, IBS-related bloating, IBS-related abdominal pain or discomfort, stool consistency, and the percentage of days with stool urgency) was greater for the patients who received rifaximin than for the patients who received placebo (Fig. 2 through 6 in the Supplementary Appendix).

RESPONSIVENESS AND CONSTRUCT VALIDITY OF PATIENT-REPORTED OUTCOMES

The response of patients with respect to adequate relief of global IBS symptoms and of IBS-related bloating was consistent with the response with respect to other IBS-related assessments. In addition, patients who had adequate relief of global IBS symptoms and of IBS-related bloating had greater improvements in daily symptom-severity scores than did patients who did not have adequate relief, regardless of study group, during each week in each study (P<0.001).

We tested the validity of using assessments of global IBS symptoms to measure changes in IBS symptoms by examining the correlation between these measures and changes in daily severity scores and bowel function; the results support the validity and usefulness of the primary end point of global IBS symptoms. Evidence for convergent validity (Spearman's correlation of 0.40 or higher) was observed between weekly adequate relief of global IBS symptoms and measures of daily symptom severity and bowel function.

SAFETY

The safety profile of rifaximin was similar to that of placebo (Table 2). Serious adverse events

were recorded in 10 patients in the rifaximin group (1.6%) and 15 patients in the placebo group (2.4%). There were no cases of *Clostridium difficile*–associated diarrhea or ischemic colitis. No deaths were reported.

DISCUSSION

Treating IBS is important because the symptoms cause substantial impairment in health-related quality of life, leading to increased use of health resources and reduced work productivity.[17-20] These two phase 3 studies showed that a short course of rifaximin leads to sustained amelioration of the symptoms of IBS without constipation in a subgroup of affected patients.

The antibiotic effect of rifaximin is the presumed mechanism for its sustained beneficial effects in patients with IBS. A response to antibiotic therapy in patients with IBS has been shown to correlate with normalization of the results of lactulose hydrogen breath tests.[8,13] However, there is debate about which antibiotic-related effect is most important. On the basis of existing data, there are three reasonable explanations: rifaximin affects gut bacteria and reduces bacterial products that negatively affect the host, the effect on gut flora reduces local mucosal engagement of bacteria such as the immune responses of the host, or the antibiotic alters both the bacteria and the host response. Whatever the final pathway, the durable effects suggest that rifaximin is affecting an underlying cause of IBS that is linked to an alteration in the intestinal microbiota.[6,7,21,22] Some patients in both of our studies did not have a response to treatment, a finding that is consistent with the results of other placebo-controlled clinical trials involving patients with IBS[23-25] and that may reflect differences in the underlying cause of the symptoms.

Similar percentages of patients in the rifaximin group and in the placebo group had adverse events. In this short-term study, the incidence of infections was similar in the two groups, and there were no cases of *C. difficile*–associated diarrhea or ischemic colitis.

In summary, the results of these two phase 3 studies showed that treatment with rifaximin at a dose of 550 mg three times daily for 14 days provides better relief of symptoms of IBS than does placebo for up to 10 weeks after completion of therapy.

Table 2. Adverse Events during the 12-Week Study.*		
Event	Rifaximin (N = 624)	Placebo (N = 634)
	number (percent)	
Adverse events†		
Headache	38 (6.1)	42 (6.6)
Upper respiratory tract infection	35 (5.6)	39 (6.2)
Abdominal pain	29 (4.6)	35 (5.5)
Nausea	27 (4.3)	24 (3.8)
Diarrhea	27 (4.3)	22 (3.5)
Nasopharyngitis	19 (3.0)	34 (5.4)
Sinusitis	17 (2.7)	16 (2.5)
Vomiting	15 (2.4)	9 (1.4)
Bronchitis	13 (2.1)	17 (2.7)
Cough	13 (2.1)	9 (1.4)
Flatulence	10 (1.6)	14 (2.2)
Back pain	10 (1.6)	15 (2.4)
Pharyngolaryngeal pain	9 (1.4)	15 (2.4)
Serious adverse events‡		
Chest pain	1 (0.2)	2 (0.3)
Breast cancer	1 (0.2)	1 (0.2)
Cholecystitis or acute cholecystitis	0	2 (0.3)
Adverse events possibly related to infection§		
Upper respiratory tract infection	35 (5.6)	39 (6.2)
Viral gastroenteritis	7 (1.1)	8 (1.3)
Gastroenteritis	6 (1.0)	3 (0.5)
Cellulitis	3 (0.5)	1 (0.2)
Pneumonia	1 (0.2)	5 (0.8)
Viral infection	1 (0.2)	4 (0.6)

* Values are pooled data from the TARGET 1 and TARGET 2 studies. Adverse events are listed in descending order of frequency in the rifaximin group.
† The adverse events listed were reported in 2% or more of the patients in either treatment group.
‡ The serious adverse events listed were reported in at least 2 of the patients in any treatment group.
§ The listed adverse events possibly related to infections are known side effects of the use of systemic antibiotics as a drug class, as well as known effects of rifaximin.

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