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Rifaximin for IBS-D: Consistent Treatment Effect Across Demographic and Baseline Disease Characteristics

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INTRODUCTION

- Patients with irritable bowel syndrome (IBS) have qualitative and quantitative alterations in the gut microbiota compared with healthy individuals[1-3]; therefore, targeting the gut microbiota may be an effective treatment for diarrhea-predominant IBS (IBS-D)
- Rifaximin, an oral, minimally absorbed antimicrobial agent, significantly improved global and individual IBS-D symptoms in 2 randomized, placebo-controlled, phase 3 studies of single, short-course (2-week) therapy (TARGET 1 and 2)[4]
- Repeat treatment with rifaximin has not been previously evaluated in a large, randomized, controlled study

OBJECTIVE

- To examine the efficacy of repeat treatment with rifaximin for IBS-D symptoms in subpopulations classified by differences in clinically relevant demographic and baseline disease characteristics (TARGET 3)

METHODS

Patient Population

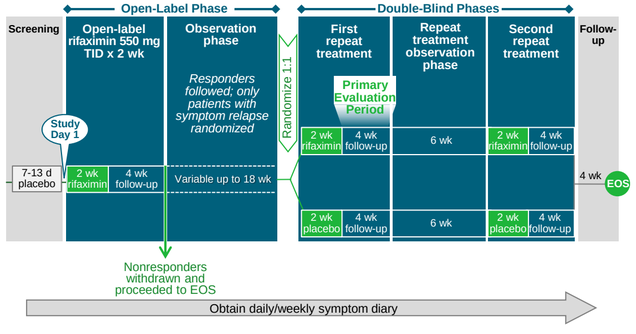
- Adults were eligible who were diagnosed with IBS-D (based on Rome III criteria) with average symptom severity scores during the screening phase of ≥3 for IBS-related abdominal pain (0 = no pain, 10 = worst possible pain you can imagine) and bloating (0 = not at all, 6 = a very great deal), and stools for ≥2 days per week meeting criteria for Bristol Stool Scale (BSS) type 6 (loose) or type 7 (watery) consistency
  - Exclusion criteria included a history of inflammatory bowel disease or taking antidiarrheals, antispasmodics, narcotics, drugs indicated for IBS, probiotics, or antibiotics within 14 days of study entry

Study Design

- Randomized, double-blind, phase 3, placebo-controlled, multicenter, multinational study
- After a 10-day placebo screening phase, patients meeting all eligibility criteria received open-label rifaximin 550 mg 3 times daily (TID) for 2 weeks, followed by a 4-week treatment-free follow-up period to assess response (Figure 1)
  - A responder was defined as a patient meeting weekly response criteria (US Food and Drug Administration composite endpoint) for both abdominal pain (≥30% decrease from baseline in mean weekly pain score) and stool consistency (≥50% decrease from baseline in number of days/week with BSS type 6 or 7 stool consistency) for ≥2 of 4 weeks during follow-up
  - Nonresponders to open-label rifaximin were withdrawn from study
- Responders were subsequently followed until relapse or for up to 18 additional weeks (observation phase)
  - Relapse was defined as loss of response for either abdominal pain or stool consistency for ≥3 out of a consecutive, rolling 4-week period during the 18-week observation phase
  - Patients who relapsed were randomly assigned (1:1) to receive two 2-week repeat treatment courses of rifaximin 550 mg TID or placebo, with repeat courses separated by 10 weeks
  - Primary endpoint: percentage of patients meeting weekly response criteria of the composite endpoint for both abdominal pain and stool consistency for ≥2 of 4 weeks during follow-up after first repeat treatment

METHODS

Figure 1. Study Design



EOS = end of study.

- Subgroup analyses were conducted for age (<65 y; ≥65 y), sex (male; female), race (white; nonwhite), body mass index (BMI; ≤30 kg/m^2; >30 kg/m^2), baseline IBS severity (based on IBS quality-of-life score: severe ≤40; nonsevere >40), and IBS disease duration (6–24 mo; 24–48 mo; 48–120 mo; ≥120 mo)

RESULTS

- Demographics and baseline disease characteristics of the 636 patients randomized to repeat treatment were similar between groups (Table 1)
- The percentage of responders (primary endpoint) was significantly greater in the rifaximin group versus the placebo group (Figure 2)
- When patient subgroups were assessed for response, repeat treatment with rifaximin was superior to placebo for multiple groups, including in patients <65 and ≥65 years, in females, in patients with nonsevere IBS, and in patients with BMI ≤30 kg/m^2 (Figure 3)
  - Nonstatistically significant differences favoring rifaximin in males, in patients with severe IBS, and patients with BMI >30 kg/m^2
- By race, the magnitude of the treatment effect was statistically significant in patients who were white, but not in patients who were nonwhite (Figure 3)
  - A treatment by race interaction analysis yielded P = 0.2, which indicated that race was not an effect modifier; the similar response rated among nonwhite patients may have been attributable to the small number of patients in that subgroup and an imbalance in baseline stool consistency severity at time of randomization (data not shown)
- Similar subgroup results favoring rifaximin were observed for the individual components of the composite endpoint, abdominal pain and stool consistency, when examined separately (data not shown)

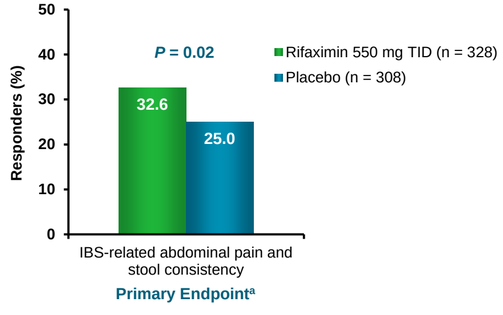
RESULTS

Table 1. Demographic and Baseline Characteristics

Characteristic		Double-Blind Population: Rifaximin 550 mg TID (n = 328)	Double-Blind Population: Placebo (n = 308)
Age, y, mean (SD)		47.9 (14.2)	45.6 (13.8)
Sex, n (%)	Male	106 (32.3)	89 (28.9)
	Female	222 (67.7)	219 (71.1)
Race, n (%)	White	273 (83.2)	262 (85.1)
	Black	37 (11.3)	31 (10.1)
	Other	18 (5.5)	15 (4.9)
Duration since first onset of IBS symptoms, y, mean (SD)		11.4 (11.0)	11.2 (10.9)
Average daily score, mean (SD)	IBS symptoms	4.2 (0.9)	4.1 (0.9)
	Bloating	4.2 (0.9)	4.1 (0.9)
	Abdominal pain	5.7 (1.7)	5.5 (1.6)
	Stool consistency	5.6 (0.8)	5.6 (0.8)
Number of daily bowel movements, mean (SD)		3.8 (2.1)	3.7 (2.1)
Days per week with stool type 6 or 7, mean (SD)		4.9 (1.8)	5.0 (1.7)
Days per week with stool urgency, mean (SD)		5.9 (1.7)	5.8 (1.7)

SD = standard deviation.

Figure 2. Percentage of Responders (First Repeat Treatment)

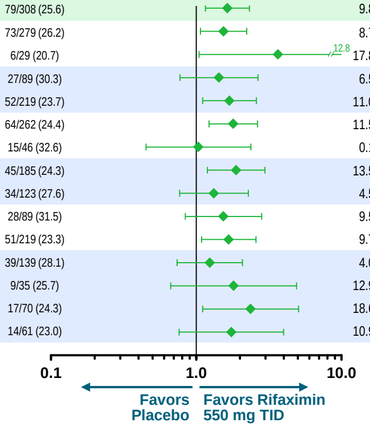


[a]Missing data were handled using the "worst case" analysis method: patients who reported <4 days of diary data in a given week were considered nonresponders for that week.

RESULTS

Figure 3. Percentage of Responders, Analyzed by Demographic and Baseline Characteristics (Primary Endpoint, First Repeat Treatment)[a]

Subgroup		Rifaximin n/N (%)	Placebo n/N (%)	Treatment Difference, %	P Value
Overall		116/328 (35.4)	79/308 (25.6)	9.8	0.005
Age	<65 y	101/289 (34.9)	73/279 (26.2)	8.7	0.020
	≥65 y	15/39 (38.5)	6/29 (20.7)	17.8	0.041
Sex	Male	39/106 (36.8)	27/89 (30.3)	6.5	0.251
	Female	77/222 (34.7)	52/219 (23.7)	11.0	0.015
Race	White	98/273 (35.9)	64/262 (24.4)	11.5	0.002
	Nonwhite	18/55 (32.7)	15/46 (32.6)	0.1	0.934
BMI	≤30 kg/m^2	74/196 (37.8)	45/185 (24.3)	13.5	0.006
	>30 kg/m^2	42/131 (32.1)	34/123 (27.6)	4.5	0.304
IBS Severity	IBS (severe)	41/100 (41.0)	28/89 (31.5)	9.5	0.156
	IBS (non-severe)	75/227 (33.0)	51/219 (23.3)	9.7	0.019
IBS Disease Duration	<24 mo	50/156 (32.1)	39/139 (28.1)	4.0	0.413
	24–48 mo	17/44 (38.6)	9/35 (25.7)	12.9	0.253
	48–120 mo	27/63 (42.9)	17/70 (24.3)	18.6	0.022
	≥120 mo	21/62 (33.9)	14/61 (23.0)	10.9	0.192



[a]Data analyzed using last observation carried forward method.
CI = confidence interval.

CONCLUSIONS

- **Response with repeat treatment generally favored rifaximin versus placebo across various demographic and baseline disease characteristics in patients with IBS-D**
- **These findings support the generalizability of the primary endpoint efficacy results in TARGET 3**

REFERENCES **1.** Kassinen A, et al. *Gastroenterology.* 2007;133(1):24-33. **2.** Carroll IM, et al. *Gut Pathog.* 2010;2(1):19. **3.** Carroll IM, et al. *Neurogastroenterol Motil.* 2012;24(6):521-530. **4.** Pimentel M, et al. *N Engl J Med.* 2011;364(1):22-32.

DISCLOSURES: PS has been a consultant, advisory board member, or member of the speakers' bureau for Avantis Pharmaceuticals, Inc., Ironwood Pharmaceuticals, and Salix Pharmaceuticals, Ltd. BC has been a consultant, advisory board member, or member of the speakers' bureau for Avantis Pharmaceuticals, Inc., IM Health, Ironwood Pharmaceuticals, Prometheus Laboratories, Inc., Salix Pharmaceuticals, Ltd., and Takeda Pharmaceuticals USA. KA, EB, CP are employees of Salix Pharmaceuticals, Ltd. WPF is an officer and employee of Salix Pharmaceuticals, Ltd.

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