POSTER NUMBER

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Safety and Tolerability of Rifaximin in a Repeat Treatment Study in Patients With IBS-D: Results From TARGET 3

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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, has a safety and tolerability profile generally comparable with placebo[4-7]
  - Data suggest that for every 846 patients who would benefit from treatment with rifaximin, 1 patient would discontinue because of an adverse event (AE; number needed to treat = 10.6; number needed to harm = 8971)[8]
- Repeat treatment with rifaximin has previously been reported to be efficacious in treating recurrent IBS-D symptoms in a large, randomized, placebo-controlled study[9]

OBJECTIVE

- To examine the safety profile of rifaximin repeat treatment (up to 3 cycles) in patients with IBS-D

METHODS

Patient Population

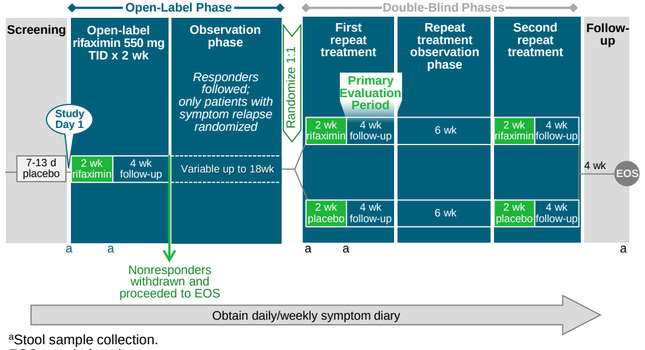
- Adults were eligible who were diagnosed with IBS-D (based on Rome III criteria) with average symptom severity scores during the screening phase of ≥3 for IBS-related abdominal pain (0 = no pain, 10 = worst possible pain you can imagine) and bloating (0 = not at all, 6 = a very great deal), and stools for ≥2 days per week that met 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 for both abdominal pain (≥30% improvement 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 the 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

METHODS

Figure 1. Study Design



[a]Stool sample collection.
EOS = end of study.

  - 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; all patients, regardless of response or relapse status after first repeat treatment, received the second repeat treatment

Safety Assessments

- Pooled safety evaluation periods
  - Open-label period: 2 weeks treatment, 4 weeks follow-up, 18 weeks observation
  - Double-blind period: first repeat treatment phase (2 weeks treatment, 4 weeks follow-up), repeat treatment observation phase (6 weeks), second repeat treatment phase (2 weeks treatment, 4 weeks follow-up), and 4 weeks follow-up
- Safety assessments included monitoring of treatment-emergent AEs, clinical laboratory tests, and vital sign measurements
- Stool samples were collected prior to and after open-label rifaximin, prior to and after the first repeat treatment, and at end of the study; prospective evaluation of stool microbiota culture and susceptibility testing were conducted with samples from a randomly selected subset of patients
  - Bacteria isolated from stool and tested for antibiotic susceptibility: *Bacteroides, Citrobacter, Clostridium, Enterobacter, Enterococcus, Escherichia, Klebsiella, Pseudomonas, Serratia,* and *Staphylococcus* species
  - Antibiotics tested: ceftazidime, ceftriaxone, ciprofloxacin, imipenem, meropenem, piperacillin/tazobactam, rifaximin, and rifampin

RESULTS

- A total of 2579 patients received open-label rifaximin (Table 1)

Table 1. Demographic and Baseline Characteristics

Characteristic	Open-Label Population: Rifaximin 550 mg TID (n = 2579)	Double-Blind Population: Rifaximin 550 mg TID (n = 328)	Double-Blind Population: Placebo (n = 308)
Age, y, mean (SD)	46.4 (13.7)	47.9 (14.2)	45.6 (13.8)
Sex, n (%)			
Male	819 (31.8)	106 (32.3)	89 (28.9)
Female	1760 (68.2)	222 (67.7)	219 (71.1)
Race, n (%)			
White	2155 (83.6)	273 (83.2)	262 (85.1)
Black	289 (11.2)	37 (11.3)	31 (10.1)
Other	135 (5.2)	18 (5.5)	15 (4.9)
Duration since first onset of IBS symptoms, y, mean (SD)	10.9 (10.8)	11.4 (11.0)	11.2 (10.9)
Number of daily bowel movements, mean (SD)	3.9 (2.2)	3.8 (2.1)	3.7 (2.1)
Days with stool type 6 or 7 in a week, mean (SD)	4.9 (1.8)	4.9 (1.8)	5.0 (1.7)
Days with stool urgency in a week, mean (SD)	5.9 (1.7)	5.9 (1.7)	5.8 (1.7)

SD = standard deviation.

- During the 24-week open-label phase, 822 (31.9%) of 2579 patients experienced an AE (Table 2)
  - Nausea was the only AE occurring in ≥2% of patients; abdominal pain, increased blood creatine phosphokinase levels, headache, influenza, nasopharyngitis, sinusitis, upper respiratory tract infection, and urinary tract infection occurred in >1% but <2% of patients
  - Constipation occurred in 15 patients (0.6%)
- 636 patients who initially responded to open-label rifaximin relapsed and were randomly assigned to repeat treatment (Table 1); the profile and incidence of AEs in the double-blind phase were comparable to what was reported during the open-label phase (Table 2)
  - Constipation was reported in 1 (0.3%) patient in the rifaximin group and 3 (1.0%) patients in placebo group
  - 1 patient developed a serious AE of *Clostridium difficile* colitis 37 days after repeat rifaximin treatment—considered by the investigators to be unrelated to study drug; although testing negative for *C difficile* toxins A and B at study entry, the patient had a history of *C difficile* infection and had completed a 10-day course of cefdinir for a urinary tract infection immediately prior to development of *C difficile* colitis

RESULTS

Table 2. Summary of Adverse Events

Adverse Event, n (%)	Open-Label Population: Rifaximin 550 mg TID (n = 2579)	Double-Blind Population: Rifaximin 550 mg TID (n = 328)	Double-Blind Population: Placebo (n = 308)
Any AE	822 (31.9)	140 (42.7)	140 (45.5)
Discontinuation due to AE	76 (2.9)	1 (0.3)	1 (0.3)
Drug-related AE	85 (3.3)	6 (1.8)	8 (2.6)
Serious AE[a]	28 (1.1)	4 (1.2)	4 (1.3)
Most common AEs[b]			
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)

[a]No serious AEs were considered by investigators to be drug-related.
[b]≥3.0% of patients in any treatment group.

- Evaluation of stool culture (please see poster Mo1268) and antibiotic susceptibility data (n = 103 in open-label; n = 73 in double-blind) indicated that up to 3 courses of rifaximin therapy did not adversely affect bacterial sensitivity to other antibiotic classes nor promote pathogenic bacterial growth; results were consistent with the clinical data indicating no increase in the occurrence of opportunistic infections with the use of rifaximin

CONCLUSION

- **No new safety signals were apparent with repeat treatment of rifaximin versus that previously reported for a single, 14-day course of therapy for IBS-D**

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. **5.** Pimentel M, et al. *Ann Intern Med.* 2006;145(8):557-563. **6.** Sharara AI, et al. *Am J Gastroenterol.* 2006;101(2):326-333. **7.** Schoenfeld P, et al. *Aliment Pharmacol Ther.* 2014;39(10):1161-1168. **8.** Shah E, et al. *Am J Med.* 2012;125(4):381-393. **9.** Lembo A, et al. Presented at: American College of Gastroenterology 2014 Annual Scientific Meeting; Philadelphia, PA; October 17-22, 2014.

DISCLOSURES: AL has served as a consultant for Salix Pharmaceuticals, Ltd. PLG, ACB, EB, and CP are employees of Salix Pharmaceuticals, Ltd. WPF is an officer and employee of Salix Pharmaceuticals, Ltd.

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