POSTER NUMBER

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Rifaximin for Improving Abdominal Pain and Bloating Symptoms in Patients With Irritable Bowel Syndrome With Diarrhea Using Modified Definitions of Pain Response

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INTRODUCTION

- Recurrent abdominal pain, a key symptom in the diagnosis of irritable bowel syndrome (IBS), and bloating are symptoms frequently experienced by patients with IBS, often leading patients to consult with a healthcare provider[1-3]
- Alterations in the gut microbiota have been associated with abdominal pain and bloating in patients with IBS[4,5]; further, alterations in the gut microbiota may affect pain frequency, duration, and intensity[6]
- Rifaximin 550-mg tablets is a nonsystemic antibiotic, indicated in the United States for the treatment of IBS with diarrhea (IBS-D) in adults,[7] and may modulate the gut microbiota of patients with IBS[8,9]

AIM

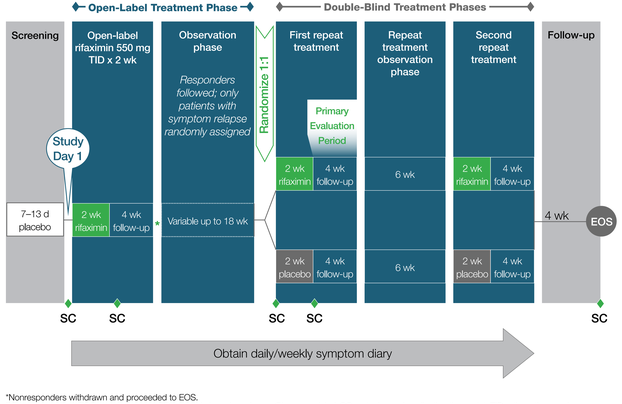
- To evaluate the efficacy of repeat rifaximin treatment in improving abdominal pain and bloating symptoms in IBS-D using modified definitions of response

METHODS

Study Design and Patient Population

- Adults with IBS with an average abdominal pain score ≥3 (scale 0-10: 0 = no pain; 10 = worst possible pain) and ≥2 days/week with Bristol Stool Scale (BSS) type 6/7 (mushy/watery) stool during a placebo-screening phase received 2 weeks of open-label rifaximin 550 mg three times daily (TID; Figure 1)

Figure 1. Study Design



*Nonresponders withdrawn and proceeded to EOS.
DB = double-blind; EOS = end of study; IBS = irritable bowel syndrome; OL = open-label; SC = stool sample collection time point; TID = three times a day.
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METHODS

- Patients with a ≥30% decrease from baseline in mean weekly abdominal pain score and ≥50% decrease from baseline in number of days/week with BSS type 6/7 stool during ≥2 of the first 4 weeks post-treatment who then experienced symptom recurrence during an 18-week, treatment-free observation period were randomly assigned in a double-blind manner to receive a second (repeat) course of rifaximin 500 mg TID for 2 weeks or a course of placebo (Figure 1)

Assessments

- For the post hoc analyses, response was defined as simultaneously meeting weekly response criteria for abdominal pain (≥30%, ≥40%, or ≥50% improvement from baseline in the weekly average abdominal pain score) and bloating (≥1-point decrease from baseline in weekly average bloating score) during ≥2 weeks of the first 4 weeks post-treatment (after open-label or double-blind treatment)
  - Response maintained during an additional 6 weeks of follow-up during the double-blind phase (ie, 10 weeks post-treatment) was considered durable response
- Abdominal pain scores were based on patient response to the daily question "In regards to your specific IBS symptom of abdominal pain, on a scale of 0-10, what was your worst IBS-related abdominal pain over the last 24 hours?"
  - Scale ranged from 0 (no pain at all) to 10 (the worst possible pain you can imagine)
- Bloating scores were based on patient response to the daily question "In regards to your specific IBS symptom of bloating, on a scale of 0-6, how bothersome was your IBS-related bloating in the last 24 hours?"
  - Scale: 0 = not at all; 1 = hardly; 2 = somewhat; 3 = moderately; 4 = a good deal; 5 = a great deal; 6 = a very great deal

Statistical Analyses

- Open-label analyses included all patients who were enrolled in the trial and received treatment, with weekly data available 4 weeks post-treatment
- Double-blind analyses included all patients in the intent-to-treat population (ie, patients randomly assigned to double-blind treatment who received ≥1 dose of treatment)
- Last observation carried forward analysis was utilized, in which missing values were replaced with the last previous nonmissing value, excepting baseline values
- In the double-blind phase, *P* values were based on chi-square tests to compare differences between rifaximin and placebo

RESULTS

Demographic and Baseline Characteristics

- 2579 patients received open-label treatment with rifaximin with mean baseline abdominal pain and bloating scores of 5.5 and 4.1, respectively (Table 1)
- Patients who experienced recurrence during the 18-week, open-label, treatment-free observation phase were randomly assigned to receive rifaximin (n=328) or placebo (n=308) in the double-blind phase of the trial

RESULTS

- Demographic and baseline characteristics were generally comparable among the 3 groups (open-label rifaximin, double-blind rifaximin, double-blind placebo; Table 1)

Table 1. Demographics and Baseline Characteristics

	Open-Label Population	Double-Blind Population	
Parameter	Rifaximin (N=2579)	Rifaximin (n=328)	Placebo (n=308)
Age, y, mean (SD)	46.4 (13.7)	47.9 (14.2)	45.6 (13.8)
Female, n (%)	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)
Average daily bowel movements, mean (SD)	3.9 (2.2)	3.8 (2.1)	3.7 (2.1)
Duration since first onset of IBS symptoms, y, mean (SD)	10.9 (10.8)	11.4 (11.0)	11.2 (10.9)
Average daily score, mean (SD)			
Abdominal pain	5.5 (1.7)	5.7 (1.7)	5.5 (1.6)
Bloating	4.1 (0.9)	4.2 (0.9)	4.1 (0.9)
Stool consistency	5.6 (0.8)	5.6 (0.8)	5.6 (0.8)
IBS symptoms	4.2 (0.9)	4.2 (0.9)	4.1 (0.9)
Days with BSS type 6 or 7 stool in a week, mean (SD)	4.9 (1.8)	4.9 (1.8)	5.0 (1.7)

BSS = Bristol Stool Scale; IBS = irritable bowel syndrome; SD = standard deviation.
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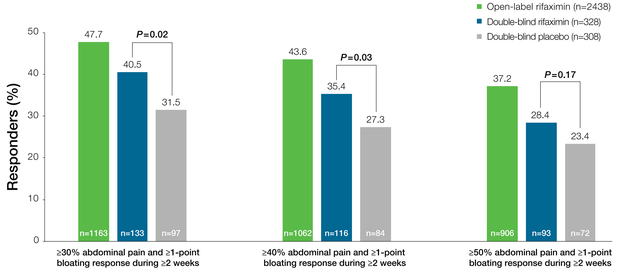
- Of the 2438 patients who received open-label rifaximin and were evaluable for efficacy, 47.7%, 43.6%, and 37.2% had a ≥30%, ≥40%, or ≥50% decrease from baseline in abdominal pain, respectively, with ≥1-point decrease from baseline in bloating scores (Figure 2)

Figure 2. Abdominal Pain and Bloating Response*



*Response defined as simultaneously meeting weekly response criteria for abdominal pain (≥30%, ≥40%, or ≥50% improvement from baseline in the weekly average abdominal pain score) and bloating (≥1-point decrease from baseline in weekly average bloating score) during ≥2 weeks of the first 4 weeks post-treatment.

- In the double-blind phase, a significantly higher percentage of rifaximin-treated patients were responders and met criteria of ≥30% and ≥40% improvement in abdominal pain plus ≥1-point decrease in bloating score compared with placebo (Figure 2)
  - Durable response was more likely in these 2 responder groups when receiving rifaximin compared with placebo (Table 2)

Table 2. Abdominal Pain and Bloating Durable Response*†

	Responders, n (%)		
Efficacy Endpoint	Rifaximin (n=328)	Placebo (n=308)	*P* value
Durable ≥30% abdominal pain and ≥1-point bloating response	87 (26.5)	58 (18.8)	0.02
Durable ≥40% abdominal pain and ≥1-point bloating response	74 (22.6)	49 (15.9)	0.04
Durable ≥50% abdominal pain and ≥1-point bloating response	53 (16.2)	41 (13.3)	0.32

*Response defined as simultaneously meeting weekly response criteria for abdominal pain (≥30%, ≥40%, or ≥50% improvement from baseline in the weekly average abdominal pain score) and bloating (≥1-point decrease from baseline in weekly average bloating score) during ≥2 weeks of the first 4 weeks post-treatment.
†Response that was maintained during an additional 6 weeks of follow-up during the double-blind phase was considered durable response (ie, 10 weeks post-treatment).

CONCLUSIONS

- **Two-week courses of rifaximin 550 mg TID provided consistent (open-label vs double-blind), significant, and durable improvement in abdominal pain and bloating symptoms versus placebo using modified definitions of IBS-D response**

REFERENCES: **1.** Lacy BE, Mearin F, Chang L, et al. *Gastroenterology.* 2016;150:1393-1407. **2.** Hungin APS, Chang L, Locke GR, Dennis EH, Barghout V. *Aliment Pharmacol Ther.* 2005;21(11):1365-1375. **3.** Ringel Y, Williams RE, Kalilani L, Cook SF. *Clin Gastroenterol Hepatol.* 2009;7(1):68-72. **4.** Malinen E, Krogius-Kurikka L, Lyra A, et al. *World J Gastroenterol.* 2010;16(36):4532-4540. **5.** Tana C, Umesaki Y, Imaoka A, et al. *Neurogastroenterol Motil.* 2010;22(5):512-519, e114-e115. **6.** Hadizadeh F, Bonfiglio F, Belheouane M, et al. *Gut.* 2018;67(4):778-779. **7.** Xifaxan® (rifaximin) tablets, for oral use [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2018. **8.** Zeber-Lubecka N, Kulecka M, Ambrozkiewicz F, et al. *Gut Microbes.* 2016;7(5):397-413. **9.** Soldi S, Vasileiadis S, Uggeri F, et al. *Clin Exp Gastroenterol.* 2015;8:309-325. **10.** Lembo A, Pimentel M, Rao SS, et al. *Gastroenterology.* 2016;151(6):1113-1121.

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