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Characterization of Long-Term Rifaximin Responders From a Phase 3, Randomized, Double-Blind, Placebo-Controlled Repeat Treatment Trial for Diarrhea-Predominant Irritable Bowel Syndrome

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INTRODUCTION

- Rifaximin is a nonsystemic antibiotic indicated in the United States for the treatment of irritable bowel syndrome (IBS) with diarrhea in adults[1]
- Phase 3, randomized, double-blind, placebo-controlled trials have demonstrated the efficacy of single[2] and repeated courses[3] of rifaximin in the treatment of diarrhea-predominant IBS (IBS-D)
  - In 2 identically designed trials, a 2-week course of rifaximin 550 mg three times daily (TID) provided adequate relief of global IBS symptoms versus placebo during ≥2 of the first 4 weeks post-treatment (P<0.001; pooled) with durable response (eg, through ≥10 weeks post-treatment)[2]
  - In a repeat treatment trial, up to three 2-week courses, rifaximin was efficacious and well tolerated in patients with IBS-D experiencing recurrent symptoms[3]
- Previous analyses have identified only duration of time since IBS symptom onset as a baseline predictor of long-term response to repeat treatment with rifaximin versus placebo[4]
- Key characteristics differentiating long-term responders to rifaximin versus those without long-term response to rifaximin are unknown

AIM

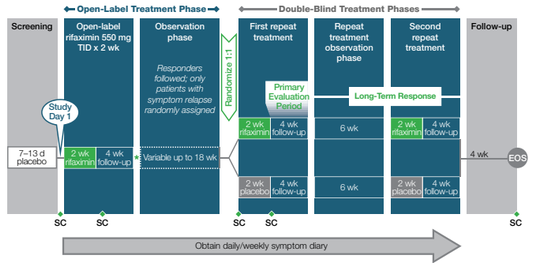
- To further characterize patients who maintain response to rifaximin repeat treatment for IBS-D symptoms

METHODS

Study Design and Patient Population[3]

- Post hoc analysis of a phase 3, randomized, double-blind, placebo-controlled trial
- Population included adults meeting Rome III criteria for IBS-D with mean daily abdominal pain score ≥3 (range, 0-10), bloating score ≥3 (range, 0-6), and ≥2 days/week with Bristol Stool Scale (BSS) type 6 or 7 stool during a placebo screening phase (**Figure 1**)
- Patients were treated with a 2-week course of open-label rifaximin 550 mg TID (**Figure 1**)
  - Patients who achieved response (ie, ≥30% decrease from baseline in the mean weekly pain score and ≥50% decrease from baseline in the number of days/week with BSS type 6 or 7 stool during ≥2 of the first 4 weeks post-treatment) were followed for up to an additional 18 weeks (observation phase)
  - Patients who experienced symptom recurrence were randomly assigned to receive two 2-week courses of double-blind rifaximin 550 mg TID or placebo; the 2 double-blind courses were separated by 10 weeks (**Figure 1**)

Figure 1. Study Design



*Nonresponders withdrawn and proceeded to EOS.
EOS = end of study; SC = stool collection; TID = three times daily.
Adapted with permission from Lembo A, et al. *Gastroenterology.* 2016;151:1113-1121.[2] © Elsevier.

METHODS

Assessments

- Long-term responder: patients with a ≥30% decrease from baseline in mean weekly pain score and ≥50% decrease from baseline in number of days/week with BSS type 6 or 7 stool for ≥2 of first 4 weeks post-treatment (primary evaluation period), which was maintained through the second 4-week follow-up phase (through 18 weeks of double-blind treatment phases)
- "No response/lack of long-term response" (NR/LLR) population: patients who did not achieve response (primary evaluation period) or those who achieved response during the primary evaluation period but did not meet criteria for "long-term" response as described above

Statistical Analyses

- Data are observed case and P values for comparison of long-term responders with non-long-term responders within the rifaximin and placebo groups were generated using the Fisher exact test (variables with character results) or 2-sample t-test (continuous variables)

RESULTS

- 290 patients with IBS-D treated with rifaximin were included in the analysis (281 patients were treated with placebo)
- Demographic and baseline characteristics were generally comparable for rifaximin groups (**Table**)
  - However, compared with the NR/LLK population, the duration since onset of IBS symptoms was significantly shorter (P=0.05) and mean number of daily bowel movements was significantly greater for long-term rifaximin responders (P=0.001)

Table. Demographics and Baseline Disease Characteristics*

	Rifaximin	
Parameter	Long-Term Responder (n=39)	NR/LLR Population (n=251)
Age, y, mean (SD)	46.8 (12.4)	48.5 (14.1)
Female sex, n (%)	27 (69.2)	171 (68.1)
Race, n (%)		
White	33 (84.6)	209 (83.3)
Black	2 (5.1)	31 (12.4)
Other	4 (10.3)	11 (4.4)
Years since onset of IBS symptoms, mean (SD)	8.3† (8.5)	12.0 (11.5)
Years since IBS diagnosis, mean (SD)	4.4 (8.1)	6.0 (9.3)
Mean daily bowel movements (SD)	4.9‡ (2.9)	3.7 (2.0)
Mean daily BSS score§ (SD)	5.8 (0.6)	5.6 (0.8)
Days/week with BSS type 6/7 stool§, mean (SD)	5.2 (1.9)	4.9 (1.8)
Days/week with stool urgency¶, mean (SD)	6.6 (1.0)	5.9 (1.8)
Mean daily abdominal pain score# (SD)	6.1 (1.6)	5.7 (1.8)
Mean daily bloating score (SD)**	4.3 (0.9)	4.2 (0.9)
Mean daily IBS symptom score†† (SD)	4.3 (0.9)	4.3 (0.9)

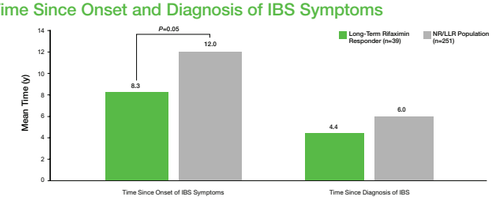
*Open-label baseline.
†P=0.05.
‡P=0.001.
§Stool consistency according to the BSS was determined by patient responses to: "On a scale of 1-7, what was the score of your least formed bowel movement in the last 24 hours?"
¶Stool urgency was calculated as 7 multiplied by (number of days felt/experienced sense of urgency with any of the bowel movements/number of days with diary data).
#Abdominal pain was determined by patient responses to: "In regards to your specific IBS symptom of abdominal pain, on a scale of 0 (no pain at all) to 10 (worst possible pain you can imagine), what was your worst IBS-related abdominal pain over the last 24 hours?"
**Bloating was determined by patient responses to: "In regards to your specific IBS symptom of bloating, on a scale of 0 (not at all to 6 (a very great deal), how bothersome was your IBS-related bloating in the last 24 hours?"
††IBS symptoms score was determined by patient responses to: "In regards to all your symptoms of IBS, on a scale of 0 (not at all) to 6 (a very great deal), how bothersome were your symptoms of IBS in the last 24 hours?"
BSS = Bristol Stool Scale; IBS = irritable bowel syndrome; NR/LLR = no response/lack of long-term response; SD = standard deviation.

- Long-term response was achieved by 39 (13.4%) patients in the rifaximin group compared with 21 (7.5%) patients in the placebo group (78.7% increase with rifaximin over placebo; P=0.01)
- At open-label baseline, compared with the NR/LLR population, long-term rifaximin responders had a significantly shorter mean duration of time since first IBS symptoms (P=0.05; **Figure 2A**) and a greater mean number of daily bowel movements (P=0.001; **Figure 2B**)
  - No significant differences were observed related to experiencing sudden onset of bowel symptoms after various types of events (**Figure 2C**)

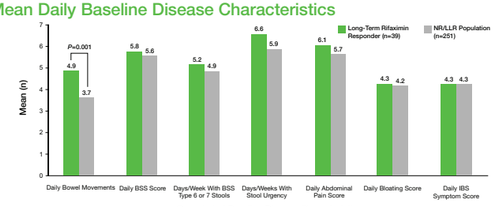
RESULTS

Figure 2. Open-Label Disease Characteristics

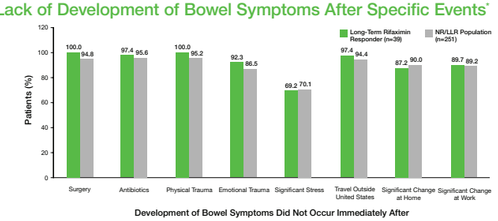
A. Time Since Onset and Diagnosis of IBS Symptoms



B. Mean Daily Baseline Disease Characteristics



C. Lack of Development of Bowel Symptoms After Specific Events*

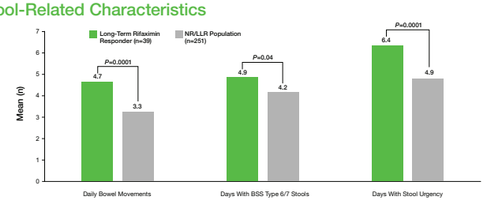


*As determined by patient responses to symptom assessment questionnaires.
BSS = Bristol Stool Scale; IBS = irritable bowel syndrome; NR/LLR = no response/lack of long-term response.

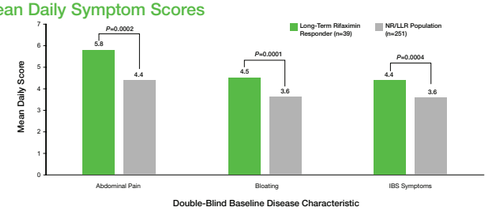
- At double-blind baseline, compared with NR/LLR population, long-term rifaximin responders had a significantly greater mean number of daily bowel movements (P=0.0001), days with BSS type 6/7 stools (P=0.04), number of days/week with stool urgency (P=0.0001; **Figure 3A**), and mean daily score for abdominal pain (P=0.0002), bloating (P=0.0001), and IBS symptoms (P=0.0004; **Figure 3B**)

Figure 3. Double-Blind Baseline Disease Characteristics

A. Stool-Related Characteristics



B. Mean Daily Symptom Scores



BSS = Bristol Stool Scale; IBS = irritable bowel syndrome; NR/LLR = no response/lack of long-term response.

CONCLUSIONS

- **More frequent (ie, number of daily bowel movements, number of days with mushy/watery stools, and number of days/week with stool urgency) and more severe symptoms (ie, abdominal pain, bloating, IBS symptoms) appeared to be differentiating factors characterizing long-term responders to repeat treatment with rifaximin**
- **Given that imbalances in the gut microbiota play a role in IBS pathophysiology,[5] the long-term efficacy of rifaximin may be mediated through its modulatory activities on the microbiota of the gastrointestinal tract**

REFERENCES: **1.** Xifaxan® (rifaximin) tablets, for oral use [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2018. **2.** Pimentel M, et al. *N Engl J Med.* 2011;364(1):22-32. **3.** Lembo A, et al. *Gastroenterology.* 2016;151(6):1113-1121. **4.** Pimentel M, et al. Presented at Digestive Disease Week 2017; May 6-8, 2017; Chicago, IL. **5.** Rajilic-Stojanovic M, et al. *Gastroenterology* 2011;141:1792-1801.

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