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Responders Analysis in Patients With Diarrhea-Predominant Irritable Bowel Syndrome Treated With Rifaximin

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INTRODUCTION

- Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurrent abdominal pain that is associated with defecation or changes in bowel movements[1]
- Rifaximin is a nonsystemic antibiotic indicated for the treatment of diarrhea-predominant IBS (IBS-D) in adults
- The safety and efficacy of rifaximin 550 mg 3 times daily (TID) for 2 weeks for the treatment of IBS-D were demonstrated in two phase 3, randomized, double-blind, placebo-controlled trials[2] and one phase 3, randomized, placebo-controlled, repeat treatment trial[3]
- For drug approval for IBS-D in the United States, it is recommended that efficacy (response) be defined by improvement in both abdominal pain and stool consistency[4]; however, trials may define the degree of improvement in these symptoms differently

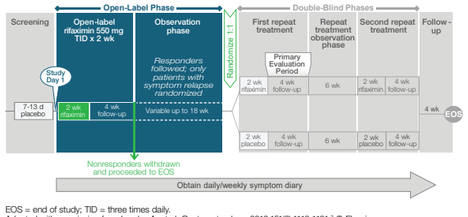
AIM

- To evaluate rifaximin efficacy for IBS-D using a modified definition of response and recurrence

METHODS

- The study included adults diagnosed with IBS-D (Rome III criteria) with average symptom severity scores during a placebo screening phase (Figure 1) of ≥3 for IBS-related abdominal pain (range, 0 = no pain; 10 = worst possible pain) and ≥3 for bloating (range, 0 = not at all; 6 = a very great deal) and with ≥2 days per week with Bristol Stool Scale (BSS) type 6 or 7 (mushy/watery) stool
- After completing the placebo screening phase, eligible patients entered an open-label treatment phase and received rifaximin 550 mg TID for 2 weeks, followed by a 4-week post-treatment period to assess response (Figure 1)

Figure 1. Study Design



EOS = end of study; TID = three times daily.
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METHODS

- As part of the original trial, responders were defined as patients simultaneously meeting weekly response criteria for abdominal pain (≥30% decrease [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) during ≥2 of the first 4 weeks post-treatment (Figure 2); nonresponders were withdrawn from the study

Figure 2. Responder Definition

Responder Definition	
Original Analysis	• Patients with ≥30% improvement from baseline in mean weekly pain score and ≥50% decrease from baseline in number of days/week with BSS type 6 or 7 stool during ≥2 of the first 4 weeks post-treatment
Post hoc analysis	• Patients with ≥30% improvement from baseline in abdominal pain score, recorded on ≥50% of the days during the first 4 weeks post-treatment, and BSS type ≤5 stool on the same days

BSS = Bristol Stool Scale.

- In the post hoc analysis, a modified definition of responders for abdominal pain and stool consistency was assessed: patients with ≥30% improvement from baseline in abdominal pain score, recorded on ≥50% of the days during the first 4 weeks post-treatment, and BSS type ≤5 stool on the same days (Figure 2)
  - If a patient did not have a bowel movement, a ≥30% improvement from baseline in abdominal pain score was considered sufficient to achieve response on that day
- Patients meeting responder criteria were followed for an additional 18 weeks or until recurrence (observation phase)
  - In the original trial, recurrence was defined as <30% decrease from baseline in mean weekly pain score or <50% decrease from baseline in number of days/week with BSS type 6 or 7 stool for ≥3 weeks of a consecutive, rolling 4-week period
  - In the post hoc analysis, abdominal pain and stool consistency recurrence was defined as <30% improvement from baseline in abdominal pain and BSS type >5 stool on ≥50% of days in a week; recurrence was assessed for each week and ≥2 consecutive weeks
  - Abdominal pain recurrence (<30% improvement from baseline in abdominal pain on ≥50% of the days in a week) was also assessed independently

RESULTS

- A total of 2579 patients with IBS-D received open-label rifaximin 550 mg TID for 2 weeks (Table)[3]
  - Of these patients, 1074 (44.1%) were responders according to the original trial definition

Table. Demographics and Baseline Characteristics

Parameter	Rifaximin 550 mg TID (n=2579)
Age, y, mean (SD)	46.4 (13.7)
Female, n (%)	1760 (68.2)
Race, n (%)	
White	2155 (83.6)
Black	289 (11.2)
Other	135 (5.2)
Duration since first onset of IBS symptoms, y, mean (SD)	10.9 (10.8)
Average daily score, mean (SD)	
Abdominal pain	5.5 (1.7)
Stool consistency	5.6 (0.8)
Bloating	4.1 (0.9)
IBS symptoms	4.2 (0.9)
Number of daily bowel movements, mean (SD)	3.9 (2.2)
Days with BSS type 6 or 7 stool in a week, mean (SD)	4.9 (1.8)
Days with bowel movement urgency in a week, mean (SD)	5.9 (1.7)

BSS = Bristol Stool Scale; IBS = irritable bowel syndrome; SD = standard deviation; TID = three times daily.
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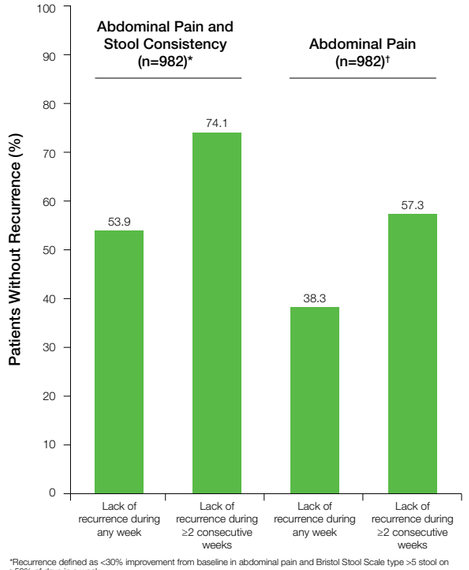
- A total of 1071 (41.5%) of the 2579 patients were classified as responders using the post hoc definition
  - 89 of the post hoc responders did not meet the original trial definition of responders, were withdrawn from the study, and did not participate in the observation phase
  - Thus, 982 of the post hoc defined responders were eligible for follow-up for an additional 18 weeks (observation phase)
- During the observation phase, the majority of the 982 patients did not experience recurrence using the post hoc composite definition of recurrence, during any week (53.9%) or during ≥2 consecutive weeks (74.1%; Figure 3)
- For abdominal pain recurrence alone, 38.3% of 982 patients did not experience recurrence during each week of the observation phase and 57.3% did not experience recurrence during ≥2 consecutive weeks (Figure 3)

Figure 3. Patients Without Recurrence During 18-Week Treatment-Free Observation Phase



*Recurrence defined as <30% improvement from baseline in abdominal pain and Bristol Stool Scale type >5 stool on ≥50% of days in a week.
†Recurrence defined as <30% improvement from baseline in abdominal pain on ≥50% of days in a week.

CONCLUSION

- **A 2-week course of rifaximin 550 mg TID was efficacious in improving symptoms of abdominal pain and stool consistency in patients with IBS-D**

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