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Rifaximin Improves Both Fecal Urgency and Stool Consistency in Adults With Irritable Bowel Syndrome With Diarrhea: A Composite Endpoint Analysis of Two Randomized, Phase 3 Trials

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BACKGROUND

- Irritable bowel syndrome (IBS) is a chronic disorder of gut-brain interaction characterized by recurrent abdominal pain and altered bowel habits[1,2]
- In patients with IBS with diarrhea (IBS-D), fecal urgency and loose stools are common, bothersome symptoms[3,4]
- Fecal urgency in patients with IBS-D is associated with more frequent and looser bowel movements,[5] and is an independent predictor of patient-reported IBS severity[6]
- Rifaximin (Xifaxan®, Salix Pharmaceuticals, Bridgewater, NJ) is indicated in the United States for the treatment of adults with IBS-D[7] and has demonstrated efficacy versus placebo for improvement of abdominal and bowel symptoms, including fecal urgency and stool consistency[8,9]

AIM

- To evaluate rifaximin treatment for simultaneously improving IBS-D symptoms of fecal urgency and loose/watery stool consistency as a unique composite bowel symptom endpoint

METHODS

- Pooled post hoc analysis of 2 identically designed, phase 3, randomized, double-blind, placebo-controlled trials[8]
- Patient population included adults with IBS-D with a daily mean stool consistency score of ≥3.5 (**Table 1**) and mean daily abdominal pain/discomfort and bloating scores of 2 to 4.5 (range: 0 [“not at all”] to 6 [“a very great deal”]) during a screening period of ≥7 days (prior to treatment initiation)
  - Additional symptom assessment included fecal urgency, based on patient response to the daily question “Have you felt or experienced a sense of urgency today?”

Table 1. Stool Consistency Score Scale

Score	Description
1	Very hard
2	Hard
3	Formed
4	Loose
5	Watery

- Patients were treated with rifaximin 550 mg three times daily or placebo for 2 weeks, followed by a 4-week treatment-free phase to assess response and an additional 6 weeks of treatment-free follow-up (ie, 10 weeks of post-treatment follow-up)
- Composite bowel symptom responders were defined as patients who simultaneously achieved a ≥30% decrease from baseline in the percentage of days with fecal urgency and had a mean weekly stool consistency score of <4 on a 5-point scale (**Table 1**)
  - Response was assessed weekly
- Sustained composite responders were defined as responders in the initial 4-week post-treatment period who also maintained the composite response for ≥3 of 6 additional treatment-free weeks of follow-up
- Data were analyzed using last observation carried forward
- *P* values were calculated using the Cochran-Mantel-Haenszel method, adjusting for analysis center

RESULTS

- A total of 1258 adults with IBS-D (rifaximin [n=624]; placebo [n=634]) were included in the analysis
- Similar values at baseline were observed for rifaximin and placebo groups for the percentage of days with fecal urgency (82%), mean daily stool consistency score (3.9), and mean number of daily bowel movements (3.0; **Table 2**)

Table 2. Demographic and Baseline Characteristics

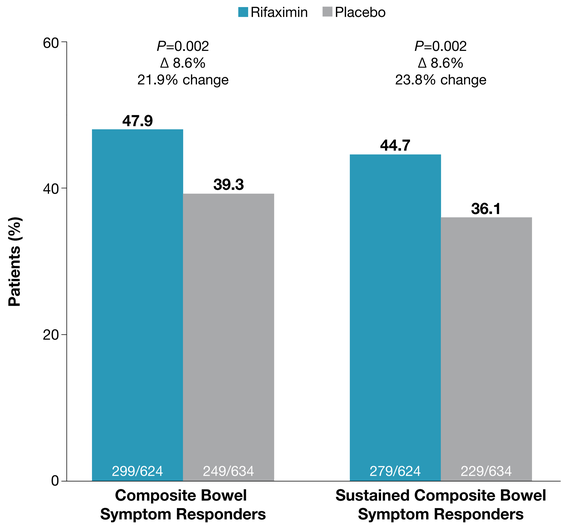
Characteristic	Rifaximin 550 mg TID (n=624)	Placebo (n=634)
Age, y, mean (SD)	46.0 (14.4)	45.9 (14.6)
Female, n (%)	462 (74.0)	447 (70.5)
Race, n (%)		
White	563 (90.2)	582 (91.8)
Black	45 (7.2)	44 (6.9)
Other	16 (2.6)	8 (1.3)
BMI, kg/m^2, mean (SD)	29.2 (6.9)	28.8 (6.7)
Days with fecal urgency, %*	81.6	82.5
Daily stool consistency score, mean (SD)†	3.9 (0.3)	3.9 (0.3)
Daily bowel movements, mean (SD)	3.0 (1.5)	3.0 (1.5)
Daily abdominal pain/discomfort score, mean (SD)‡	3.2 (0.7)	3.3 (0.7)
Daily bloating score, mean (SD)‡	3.3 (0.8)	3.3 (0.7)

*Calculated using the following formula: 100 × (number of days with a sense of urgency with any bowel movement ÷ number of days with bowel movements).
†5-point scale (1 = “very hard”; 2 = “hard”; 3 = “formed”; 4 = “loose”; 5 = “watery”).
‡7-point scale (0 = “not at all”; 2 = “somewhat”; 3 = “moderately”; 4 = “a good deal”; 5 = “a great deal”; 6 = “a very great deal”).
BMI = body mass index; TID = three times daily.

RESULTS

- A significantly greater percentage of patients treated with rifaximin were composite bowel symptom responders for ≥2 of the first 4 weeks post-treatment compared with placebo (47.9% vs 39.3%, respectively; *P*=0.002; **Figure 1**)

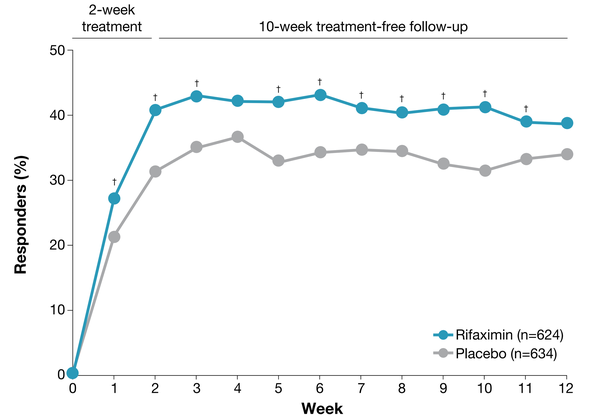
Figure 1. Composite Bowel Symptom Responders* and Sustained Composite Bowel Symptom Responders†



*Patients who simultaneously achieved a ≥30% decrease from baseline in the percentage of days with fecal urgency and a mean weekly average stool consistency score of <4 for ≥2 of the first 4 weeks post-treatment.
†Patients who simultaneously achieved a ≥30% decrease from baseline in the percentage of days with fecal urgency and a mean weekly average stool consistency score of <4 for ≥2 of the first 4 weeks post-treatment who also maintained both responses for ≥3 of 6 additional treatment-free weeks (up to 10 weeks post-treatment).

- A significantly greater percentage of patients treated with rifaximin who were composite bowel symptom responders during ≥2 of the first 4 weeks post-treatment maintained response during ≥3 of the additional 6 weeks of treatment-free follow-up (up to 10 weeks post-treatment) versus placebo group (44.7% vs 36.1%, respectively; *P*=0.002; **Figure 1**)
- In addition, a higher percentage of patients receiving rifaximin were composite bowel symptom responders compared with placebo when analyzed weekly (**Figure 2**)

Figure 2. Percentage of Composite Bowel Symptom Responders* by Week



*Patients who simultaneously achieved a ≥30% decrease from baseline in percentage of days with fecal urgency and a mean weekly stool consistency score of <4.
†*P*<0.05 vs placebo.

CONCLUSION

- **A 2-week course of daily rifaximin treatment significantly and simultaneously improved fecal urgency and stool consistency compared with placebo in adults with IBS-D**

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