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Efficacy of Rifaximin on Bowel Movement Urgency in Patients With Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D): A Pooled Analysis of Three Phase 3 Trials

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BACKGROUND

- Rifaximin is an oral nonsystemic antibiotic that targets the gastrointestinal tract and is associated with a low risk of clinically relevant bacterial antibiotic resistance when used as directed; it is approved for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D) in adults, and the safety and efficacy of rifaximin in IBS-D have been demonstrated in three phase 3 trials[1-3]
- Bowel movement urgency is a common symptom in patients with IBS and is reported by approximately 80% of patients with IBS-D[2,4,5]
  - In a 2015 survey, 40% of individuals with IBS-D indicated that they experience urgency ≥4–6 days per week[5]
- Bowel movement urgency is strongly and significantly associated with the severity of IBS, particularly in IBS-D[6]
- In addition, bowel movement urgency is associated with impaired quality of life in patients with IBS[7,8]

AIM

- To further characterize improvements in bowel movement urgency after 2 weeks of treatment with rifaximin in patients with IBS-D

METHODS

Patient Population

- Adults diagnosed with IBS-D (confirmed by Rome II criteria for Trials 1 and 2 and Rome III criteria for Trial 3 [TARGET 3]) and did not have adequate relief of global IBS symptoms and bloating during a screening phase were eligible for participation
- Patients were also required to have average symptom severity scores for both abdominal pain and bloating during a screening phase between 2 and 4.5 (Trials 1 and 2; scale 0–6; 0 = not at all, 6 = a very great deal) or ≥3 (Trial 3; abdominal pain scale 0–10; 0 = no pain, 10 = worst possible pain; bloating scale 0–6; 0 = not at all, 6 = a very great deal)[2,3,9]
- In addition, eligible patients were required to rate their average daily stool consistency during the previous 7 days as ≥3.5 on a 5-point scale (1 = very hard, 2 = hard, 3 = formed, 4 = loose, 5 = watery) for Trials 1 and 2[2]; for Trial 3, patients were required to have experienced loose stools for ≥2 days per week with Bristol Stool Scale type 6 (loose) or 7 (watery) stool consistency[3]

Study Design

- Post hoc, pooled analysis of data from 3 randomized, double-blind, phase 3, placebo-controlled, multicenter studies
- In Trials 1 and 2, patients were randomly assigned to receive rifaximin 550 mg or placebo 3 times daily (TID) for 2 weeks, followed by a 4-week treatment-free follow-up period to evaluate efficacy; in Trial 3, patients were randomly assigned to receive rifaximin 550 mg or placebo TID for 2 weeks only if they had previously responded to a 2-week course of open-label rifaximin 550 mg TID and developed IBS symptom recurrence during 18 weeks post-treatment
  - Urgency was determined daily using an interactive computerized response system with the patient responding yes or no to the question "Have you felt or experienced a sense of urgency today?" in Trials 1 and 2 and "Have you felt or experienced a sense of urgency in the last 24 hours with any of your bowel movements?" in Trial 3
  - Bowel movement urgency response was defined as ≥30% improvement from baseline in the percentage of days with urgency for ≥2 of the first 4 weeks post-treatment
  - Weekly bowel movement response (≥30% improvement from baseline in the percentage of days with bowel movement urgency) was also evaluated
- Logistic regression was used to analyze the overall treatment effect on response; a general estimating equation model was used to analyze treatment effects by week

RESULTS

- Pooled analysis included 1894 patients (rifaximin, n=952; placebo, n=942) with IBS-D (Table)
- The mean baseline days per week with bowel movement urgency were the same (5.8 days) for both treatment groups

Table. Demographic and Baseline Characteristics

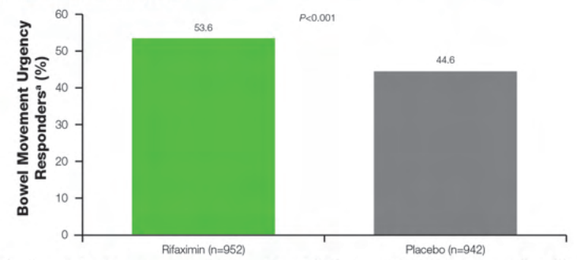
Characteristic	Rifaximin 550 mg TID (n=952)	Placebo TID (n=942)
Age, y, mean (SD)	46.6 (14.3)	45.8 (14.3)
Sex, n (%)		
Male	268 (28.2)	276 (29.3)
Female	684 (71.8)	666 (70.7)
Race, n (%)		
White	836 (87.8)	844 (89.6)
Black	82 (8.6)	75 (8.0)
Other	34 (3.6)	23 (2.4)
Duration since first onset of IBS symptoms, y, mean (SD)	11.3 (10.6)	11.5 (11.1)
Average daily score, mean (SD)a		
Global IBS symptoms	3.7 (0.9)	3.6 (0.8)
Bloating	3.6 (0.9)	3.5 (0.9)
Abdominal pain	4.1 (1.6)	4.0 (1.5)
Stool consistency	4.5 (1.0)	4.5 (0.9)
Number of daily bowel movements, mean (SD)	3.2 (1.7)	3.2 (1.7)
Days per week with bowel movement urgency, mean (SD)	5.8 (1.6)	5.8 (1.6)

[a]Scale score ranges: abdominal pain, 0–6 (Trials 1 and 2) or 0–10 (Trial 3); bloating, 0–6; stool consistency, 1–7; and global IBS symptoms, 0–6.
IBS = irritable bowel syndrome; SD = standard deviation; TID = three times daily.

RESULTS

- A significantly greater percentage of patients receiving rifaximin were bowel movement urgency responders compared with placebo (odds ratio, 1.4; 95% confidence interval, 1.2–1.7; $P<0.001$; Figure 1)

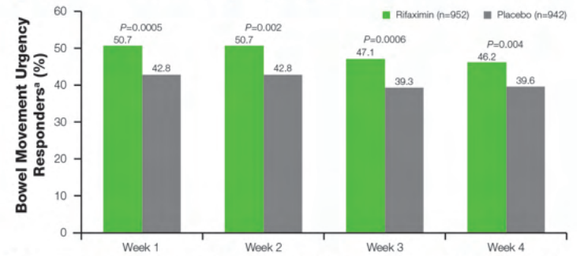
Figure 1. Bowel Movement Urgency Responders During 4-Week Post-Treatment Period[a]



[a]Bowel movement urgency responders were defined as patients with ≥30% improvement from baseline in the percentage of days with urgency during ≥2 of the first 4 weeks post-treatment.

- Furthermore, the percentage of bowel movement urgency responders was significantly greater with rifaximin versus placebo during the first week post-treatment (Week 1; $P=0.0005$; Figure 2)
  - This significant difference was maintained during Weeks 2 through 4 post-treatment

Figure 2. Bowel Movement Urgency Responders by Post-Treatment Week[a]



[a]Bowel movement urgency responders were defined as patients with ≥30% improvement from baseline in the percentage of days with urgency during that week.

CONCLUSION

- **This pooled analysis confirms that rifaximin 550 mg TID for 2 weeks significantly improves bowel movement urgency versus placebo in adults with IBS-D**
- **Treatment response was observed as early as Week 1 post-treatment and maintained through at least 4 weeks, suggesting that the effects of a 2-week course of rifaximin on bowel movement urgency persists for at least 4 weeks post-treatment**

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