A New Trisymptom Composite Endpoint to Evaluate the Efficacy of Rifaximin for Multiple Symptoms of Irritable Bowel Syndrome With Diarrhea: a Pooled Analysis of Two Randomized, Phase 3 Trials

Brian E. Lacy, MD, PhD[1]; Gregory S. Sayuk, MD, MPH[2]; Hetal A. Karsan, MD[3]; Christopher Allen, MS[4]; Zeev Heimanson, PharmD[4]; Darren M. Brenner, MD[5]

[1]Mayo Clinic, Jacksonville, FL; [2]St. Louis Veterans Affairs Medical Center, St. Louis, MO; [3]Atlanta Gastroenterology Associates, Atlanta, GA; [4]Salix Pharmaceuticals, Bridgewater, NJ; [5]Northwestern University, Chicago, IL

INTRODUCTION

- Patients with irritable bowel syndrome with diarrhea (IBS-D) experience multiple symptoms in addition to altered bowel habits; specifically, abdominal pain/discomfort, bloating, and bowel movement (BM) urgency[1]
- Therefore, it is paramount that IBS-D management strategies identify treatments that effectively address the symptoms that typify the disorder
- Rifaximin (Xifaxan, Salix Pharmaceuticals, Bridgewater, NJ) is indicated in the United States for the treatment of adults with IBS-D[2]
- The efficacy and safety of rifaximin have been demonstrated in multiple randomized, double-blind, placebo-controlled phase 3 trials[3,4]
  - Rifaximin improved individual symptoms of abdominal pain/discomfort, bloating, and BM urgency[3,4]

OBJECTIVE

- To evaluate improvement utilizing a novel trisymptom composite endpoint (abdominal pain/discomfort, bloating, BM urgency) in patients with IBS-D

METHODS

- Pooled post hoc analysis of 2 identically designed, phase 3, randomized, double-blind, placebo-controlled trials (ClinicalTrials.gov identifiers NCT00731679 and NCT00724126)[3]
- Adults with IBS-D received rifaximin 550 mg three times daily (TID), or placebo, for 2 weeks, followed by a 4-week, treatment-free period to assess response[3]
- Abdominal pain/discomfort and bloating were separately rated daily using a 7-point Likert scale ranging from 0 (“not at all”) to 6 (“a very great deal”)[3]
- BM urgency was assessed daily, based on patients’ yes/no responses to the question, “Have you felt or experienced a sense of urgency today?”
- Trisymptom composite responders were defined as patients who simultaneously achieved a ≥30% decrease from baseline in weekly mean abdominal pain/discomfort and bloating scores, and a ≥30% decrease from baseline in the percentage of days with BM urgency for ≥2 of the first 4 weeks post-treatment
  - An identical analysis was performed using an overall threshold of ≥40% (ie, ≥40% decrease from baseline in all 3 symptoms)
- Data were analyzed using last observation carried forward, and *P* values were calculated using Cochrane-Mantel-Haenszel method, adjusting for analysis center

RESULTS

- 1258 patients (rifaximin, n=624; placebo, n=634) were included in the analysis (**Table**)
  - Overall, patients had a mean (standard deviation) age of 45.9 (14.5) years, and 72.3% were female

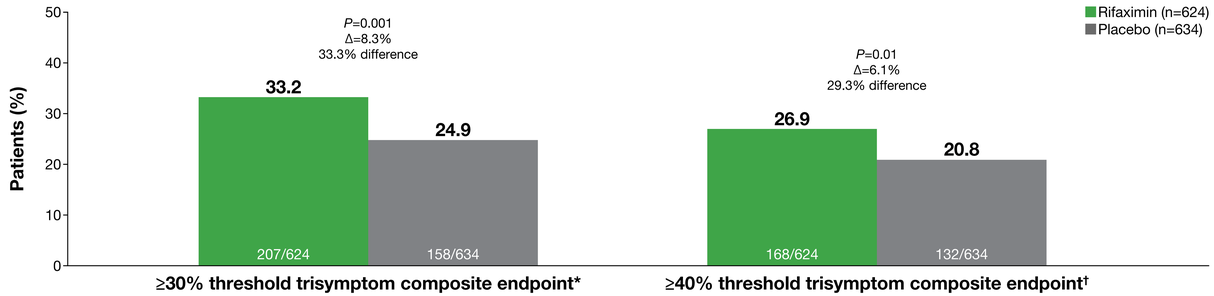
Table. Demographic and Baseline Disease Characteristics

Characteristic	Rifaximin (n=624)	Placebo (n=634)
Age, y, mean (SD)	46.0 (14.4)	45.9 (14.6)
Female sex, n (%)	462 (74.0)	447 (70.5)
White race, n (%)	563 (90.2)	582 (91.8)
BMI, kg/m^2, mean (SD)	29.2 (6.9)	28.8 (6.7)
Daily stool consistency score, mean (SD)*	3.9 (0.3)	3.9 (0.3)
Daily abdominal pain/discomfort score, mean (SD)†	3.3 (0.7)	3.3 (0.7)
Daily bloating score, mean (SD)†	3.3 (0.8)	3.3 (0.7)
Days with BM urgency, %, mean (SD)‡	81.6 (22.5)	82.5 (22.4)

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

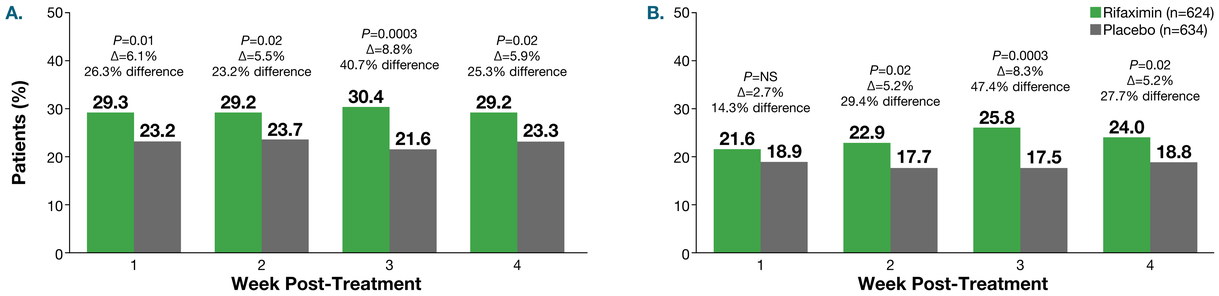
- As previously reported, a significantly greater percentage of patients treated with rifaximin had adequate relief of global IBS symptoms (patient response to: “In regard to all your symptoms of IBS, as compared with the way you felt before you started the study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms?”) during ≥2 of the first 4 weeks post-treatment compared with placebo (40.7% vs 31.7%, respectively; *P*<0.001)[3]
- In the current analysis, for the trisymptom composite endpoint with either the ≥30% or ≥40% threshold, a statistically significantly greater percentage of patients treated with rifaximin were responders compared with placebo (**Figure 1**)
- A statistically significantly greater percentage of patients achieved response (≥30% trisymptom threshold) with rifaximin compared with placebo as early as 1 week post-treatment (**Figure 2A**), with significance maintained ≥5 weeks post-treatment
- For the trisymptom endpoint (≥40% threshold), response was achieved in a significantly greater percentage of patients treated with rifaximin versus placebo as early as 2 weeks post-treatment, and maintained through 4 weeks post-treatment (**Figure 2B**)

Figure 1. IBS-D Trisymptom Composite Responders (≥30%* or ≥40%† Thresholds)



*≥30% decrease from baseline in weekly mean abdominal pain/discomfort score AND ≥30% decrease from baseline in mean bloating score AND ≥30% improvement from baseline in percentage of days with BM urgency for ≥2 of first 4 weeks post-treatment. †≥40% decrease from baseline in weekly mean abdominal pain/discomfort score AND ≥40% decrease from baseline in mean bloating score AND ≥40% improvement from baseline in percentage of days with BM urgency for ≥2 of first 4 weeks post-treatment. BM = bowel movement; IBS-D = irritable bowel syndrome with diarrhea.

Figure 2. Treatment Response Using the (A) ≥30% Threshold* or (B) ≥40% Threshold† Definition, By Week Post-Treatment Period



*Response defined as ≥30% simultaneous improvement from baseline in weekly average pain score, weekly average bloating score, and percentage of days with bowel movement urgency. †Response defined as ≥40% simultaneous improvement from baseline in weekly average pain score, weekly average bloating score, and percentage of days with bowel movement urgency. NS = not significant.

CONCLUSIONS

- **Using a unique trisymptom endpoint, a 2-week course of rifaximin for IBS-D significantly and simultaneously improved numerous abdominal symptoms versus placebo; these responses occurred shortly after treatment and were maintained over time**
- **These results suggest that rifaximin is effective for more than just primary IBS-D symptoms**

REFERENCES: 1. Lacy BE, Mearin F, Chang L, et al. *Gastroenterology.* 2016;150(6):1393-1407. **2.** Xifaxan tablets, for oral use. Package insert. Salix Pharmaceuticals; 2020. **3.** Pimentel M, Lembo A, Chey WD, et al. *N Engl J Med.* 2011;364(1):22-32. **4.** Lembo A, Pimentel M, Rao SS, et al. *Gastroenterology.* 2016;151(6):1113-1121.

ACKNOWLEDGMENTS: The trials and current analyses were supported by Salix Pharmaceuticals. Technical editorial and medical writing assistance were provided under direction of the authors by Mary Beth Moncrief, PhD, and Sophie Bolick PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this assistance was provided by Salix Pharmaceuticals.

DISCLOSURES: BEL reports serving as an advisory board member for Allakos Inc., Arena Pharmaceuticals, Inc., Ironwood Pharmaceuticals, Inc., Salix Pharmaceuticals, and Sanofi. GSS reports serving as a consultant for AbbVie Inc., and Ironwood Pharmaceuticals, Inc.; and serving on the speakers’ bureau for AbbVie Inc., Ironwood Pharmaceuticals, Inc., and Salix Pharmaceuticals. HAK reports having served as an advisor, consultant, or speaker for AbbVie Inc., Alexion Pharmaceuticals, Gilead Sciences, Inc., Kaleido Biosciences, Inc., Mallinckrodt, and Salix Pharmaceuticals. CA and ZH are employees of Salix Pharmaceuticals. DMB reports having served as a consultant, advisor, and/or speaker for AbbVie Inc., Alnylam Pharmaceuticals, Inc., AlphaSigma, Ardelyx, Arena Pharmaceuticals, Inc., Gemelli Biotech, Ironwood Pharmaceuticals, Inc., Mahana, QoL Medical, LLC, RedHill Biopharma Ltd., Salix Pharmaceuticals, and Takeda Pharmaceutical Co., Ltd.

AAFP FMX 2022 • September 20–23, 2022 • Washington, DC

Research funded by: Salix Pharmaceuticals