POSTER NUMBER 130

Association Between Symptoms in Irritable Bowel Syndrome With Diarrhea: A Pooled Correlation and Tricomposite Endpoint Analysis of Two Phase 3, Randomized, Placebo-Controlled, Rifaximin Trials

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BACKGROUND AND AIM

- Criteria for establishing a diagnosis of irritable bowel syndrome (IBS) include recurrent abdominal pain and altered stool consistency/frequency; however, other symptoms (eg, bloating) are common and bothersome[1-3]
- Rifaximin (Xifaxan®, Salix Pharmaceuticals, Bridgewater, NJ) is indicated in the United States for the treatment of adults with IBS with diarrhea (IBS-D)[4] and has been shown to improve multiple IBS-D symptoms, including abdominal pain, bloating, and stool consistency[5,6]
- **Aim:** to evaluate rifaximin effectiveness in improving a unique trisymptom ("tricomposite") endpoint (abdominal pain/discomfort, bloating, bowel movement [BM] urgency) and to assess potential relationships between improvement between global and individual symptom improvements in patients with IBS-D

METHODS

- Pooled post hoc analysis of two phase 3, identically designed, randomized, double-blind, placebo-controlled trials[5]
- Population included adults with IBS-D with mean daily abdominal pain/discomfort and bloating scores, rated separately, of 2 to 4.5 and a daily mean stool consistency score of ≥3.5 (evaluated during a ≥7-day screening period)
  - Daily abdominal pain/discomfort and bloating assessed separately using a 7-point scale: 0 ("not at all") to 6 ("a very great deal")
  - Daily stool consistency assessed using a 5-point scale: 1 ("very hard") to 5 ("watery")
- Patients were randomly assigned to receive rifaximin 550 mg three times daily or placebo for 2 weeks, followed by a 10-week follow-up period
- BM urgency was assessed daily, based on patients' yes/no responses to "Have you felt or experienced a sense of urgency today?"
- Global IBS symptoms were also assessed daily ("In regards to all your symptoms of IBS; on scale of 0 ["not at all"] to 6 ["a very great deal"], how bothersome were your symptoms of IBS today?")
- **Tricomposite responders:** defined as patients with ≥30% decrease from baseline in both weekly mean abdominal pain/discomfort and bloating scores and ≥30% decrease from baseline in the percentage of days with BM urgency, for ≥2 of first 4 weeks post-treatment[7]
- Pearson correlation analyses compared change from baseline in abdominal pain/discomfort, bloating, stool consistency, or BM urgency and global IBS symptoms (overall [12 weeks] and by week)
  - Coefficient (*r*) value of >0.70 to 1.00 was considered a strong positive correlation (>0.50-0.70 [moderate] and ≤0.50 [weak-to-negligible])

RESULTS

- Pooled analysis included 1258 patients (rifaximin [n=624], placebo [n=634]; **Table 1**)
  - Baseline scores for mean daily abdominal pain and bloating and the percentage of days with BM urgency were comparable between the 2 groups

Table 1. Demographic and Baseline Characteristics

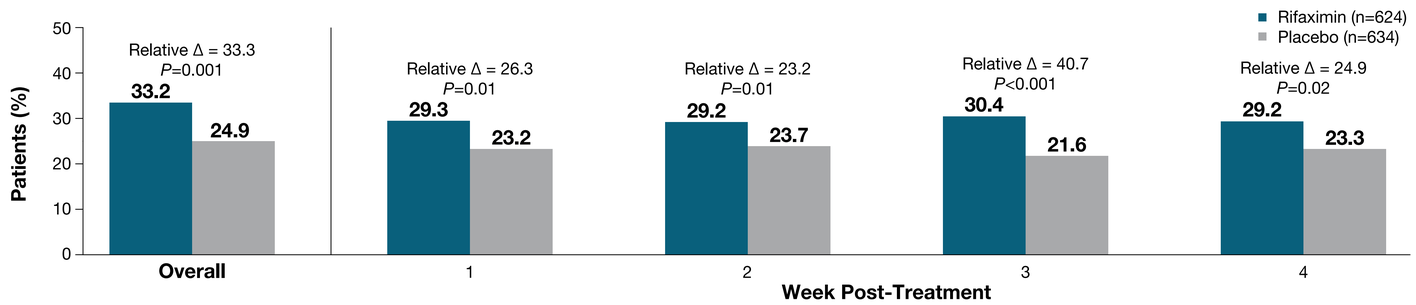
Parameter	Rifaximin (n=624)	Placebo (n=634)
Age, y, mean (SD)	46.0 (14.4)	45.9 (14.6)
Female, n (%)	462 (74.0)	447 (70.5)
White race, n (%)	563 (90.2)	582 (91.8)
BMI, kg/m², mean (SD)	29.2 (6.9)	28.8 (6.7)
Daily abdominal pain/discomfort score, mean (SD)*	3.3 (0.7)	3.3 (0.7)
Daily bloating score, mean (SD)*	3.3 (0.8)	3.3 (0.7)
Daily stool consistency score, mean (SD)†	3.9 (0.3)	3.9 (0.3)
Days with BM urgency, %, mean (SD)‡	81.6 (22.5)	82.5 (22.4)

*7-point scale (0 = not at all; 1 = hardly; 2 = somewhat; 3 = moderately; 4 = a good deal; 5 = a great deal; 6 = a very great deal).
†5-point scale (1 = very hard; 2 = hard; 3 = formed; 4 = loose; 5 = watery).
‡Calculated using the following formula: 100 × (number of days with sense of urgency with any bowel movement ÷ number of days with bowel movement).
BM = bowel movement; BMI = body mass index.
Data from Pimentel M, et al. *N Engl J Med.* 2011;364(1):22-32; and Lacy BE, et al. *Clin Ther.* 2023;45(3):198-209.[5,7]

- A significantly greater percentage of patients treated with rifaximin were tricomposite responders compared with placebo (33.2% [207/624] vs 24.9% [158/634]; *P*=0.001; **Figure 1**)
  - Significant differences favoring rifaximin occurred within 1 week post-treatment and remained statistically significant through at least 4 weeks of post-treatment

RESULTS

Figure 1. IBS-D Tricomposite Responders*



*Patients with ≥30% simultaneous improvement from baseline in weekly mean abdominal pain/discomfort score, weekly mean bloating score, and percentage of days with BM urgency overall (≥2 of first 4 weeks post-treatment) and by post-treatment week. Relative change calculated as (rifaximin value – placebo value)/placebo value.
BM = bowel movement; IBS-D = irritable bowel syndrome with diarrhea.
Data from Lacy BE, et al. *Clin Ther.* 2023;45(3):198-209.[7]

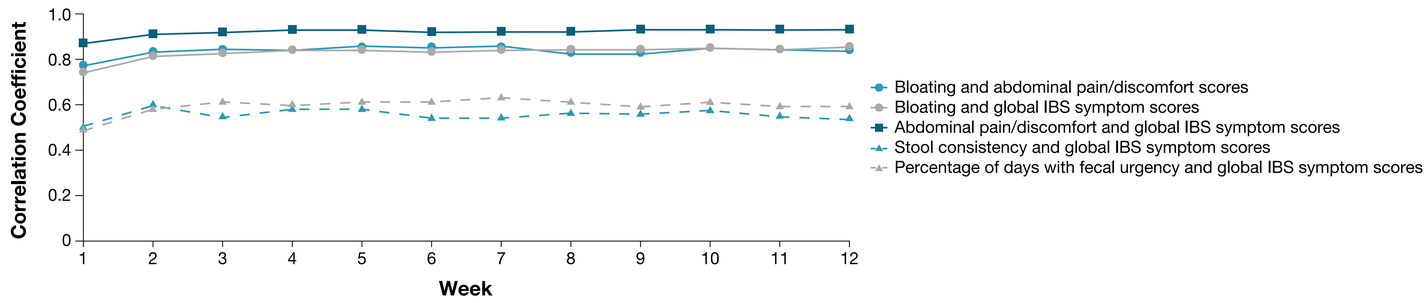
- Strong positive correlations were observed for changes from baseline in weekly average symptom scores over time for bloating and abdominal pain/discomfort, bloating and global IBS symptoms, and abdominal pain/discomfort and global IBS symptoms, whether calculated as a mean weekly or daily symptom score (*r*≥0.78; **Table 2**)
  - Correlation was moderate between global IBS symptom scores and both stool consistency score and the percentage of days with BM urgency (*r*≤0.60)
- Weekly comparison of correlations between the various symptoms was consistent for Weeks 2 through 12 (**Figure 2**)

Table 2. Overall Correlations Between Change From Baseline in IBS Symptom Scores

	Pearson Correlation Coefficient, *r*	
Symptom Comparison	Weekly Average Symptom Scores	Daily Symptom Scores
Bloating and abdominal pain/discomfort scores	0.84	0.78
Bloating and global IBS symptom scores	0.84	0.79
Abdominal pain/discomfort and global IBS symptom scores	0.92	0.88
Stool consistency and global IBS symptom scores	0.56	0.53
Percentage of days with BM urgency and global IBS symptom scores	0.60	—*

*Due to definition, not assessed daily.
BM = bowel movement; IBS = irritable bowel syndrome.

Figure 2. Correlation Coefficients for Weekly Average Symptom Score Comparisons, by Week



IBS = irritable bowel syndrome.

CONCLUSIONS

- Rifaximin has substantial activity beyond IBS-D cardinal symptoms (ie, abdominal pain and diarrhea), as shown by simultaneous improvement in multiple symptoms measured using a tricomposite endpoint analysis
- Bloating and abdominal pain/discomfort were highly correlated and may share a common etiology, such as visceral hypersensitivity, whereas stool consistency and BM urgency showed weaker correlations
- Bloating and abdominal pain/discomfort may also have a greater effect on patient overall perception of IBS symptoms than altered stool consistency or BM urgency
- Therefore, rifaximin should be considered as a therapeutic option for bloating in addition to abdominal pain/discomfort and diarrhea

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ACKNOWLEDGMENTS: The 2 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: KS reports serving as a consultant to Anji Pharmaceuticals Inc., Ardelyx, Inc., Gelesis, GI Supply, Restalsis, and Sanofi. BEL reports serving as an advisory board member for Allakos, CinDome Pharma, Gemelli Biotech Corp., Ironwood Pharmaceuticals, Inc., Salix Pharmaceuticals, and Sanofi. GSS reports serving as a consultant for AbbVie, Ardelyx, Inc., Ironwood Pharmaceuticals, Inc., and Rome Foundation; and serving on the speakers' bureau for Ardelyx, Inc., AbbVie, GI Health Foundation, Ironwood Pharmaceuticals, Inc., and Salix Pharmaceuticals. SSCR reports receiving research funding from Salix Pharmaceuticals. HAK reports serving as an advisor or speaker for AbbVie, Alexion, Ardelyx, Inc., Commonwealth Diagnostics International, Inc., Gemelli Biotech Corp., Gilead Sciences, Inc., Intercept Pharmaceuticals, Inc., Mallinckrodt, and Salix Pharmaceuticals. LN reports having nothing to disclose. TNL reports having nothing to disclose. CA and ZH are employees of Salix Pharmaceuticals. DMB reports having served as a consultant, advisor, and/or speaker for AbbVie, Alnylam Pharmaceuticals, Anji Pharmaceuticals Inc., Ardelyx, Inc., Arena Pharmaceuticals, Bayer, Gemelli Biotech Corp., Ironwood Pharmaceuticals, Inc., Mahana Therapeutics, Owlstone Medical Ltd., QoL Medical LLC, RedHill Biopharma Ltd., Salix Pharmaceuticals, Takeda Pharmaceutical Co., and Vibrant Pharma Inc.

American Neurogastroenterology & Motility Society Annual Meeting • August 11–13, 2023 • Austin, TX

Research funded by: Salix Pharmaceuticals