

# 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<sup>1</sup>; Gregory S. Sayuk, MD, MPH<sup>2</sup>; Hetal A. Karsan, MD<sup>3</sup>; Christopher Allen, MS<sup>4</sup>; Zeev Heimanson, PharmD<sup>4</sup>; Darren M. Brenner, MD<sup>5</sup>

<sup>1</sup>Mayo Clinic, Jacksonville, FL; <sup>2</sup>St. Louis Veterans Affairs Medical Center, St. Louis, MO; <sup>3</sup>Atlanta Gastroenterology Associates, Atlanta, GA; <sup>4</sup>Salix Pharmaceuticals, Bridgewater, NJ; <sup>5</sup>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<sup>1</sup>
- 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<sup>2</sup>
- The efficacy and safety of rifaximin have been demonstrated in multiple randomized, double-blind, placebo-controlled phase 3 trials<sup>3,4</sup>
  - Rifaximin improved individual symptoms of abdominal pain/discomfort, bloating, and BM urgency<sup>3,4</sup>

## 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)<sup>3</sup>
- 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<sup>3</sup>
- 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”)<sup>3</sup>
- 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  $\geq 30\%$  decrease from baseline in weekly mean abdominal pain/discomfort and bloating scores, and a  $\geq 30\%$  decrease from baseline in the percentage of days with BM urgency for  $\geq 2$  of the first 4 weeks post-treatment
  - An identical analysis was performed using an overall threshold of  $\geq 40\%$  (ie,  $\geq 40\%$  decrease from baseline in all 3 symptoms)
- Data were analyzed using last observation carried forward, and *P* values were calculated using Cochran-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

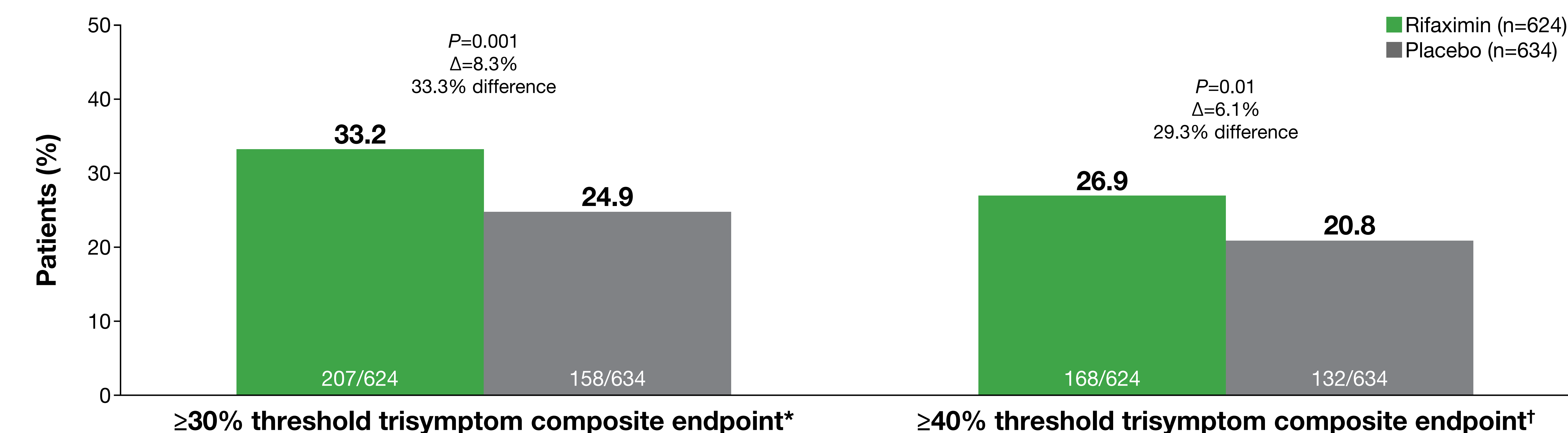
Table. Demographic and Baseline Disease Characteristics

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 <sup>2</sup> , 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:  $100 \times (\text{number of days with a sense of urgency with any BM} \div \text{number of days with BM})$ . BM = bowel movement; BMI = body mass index; SD = standard deviation; TID = three times daily.

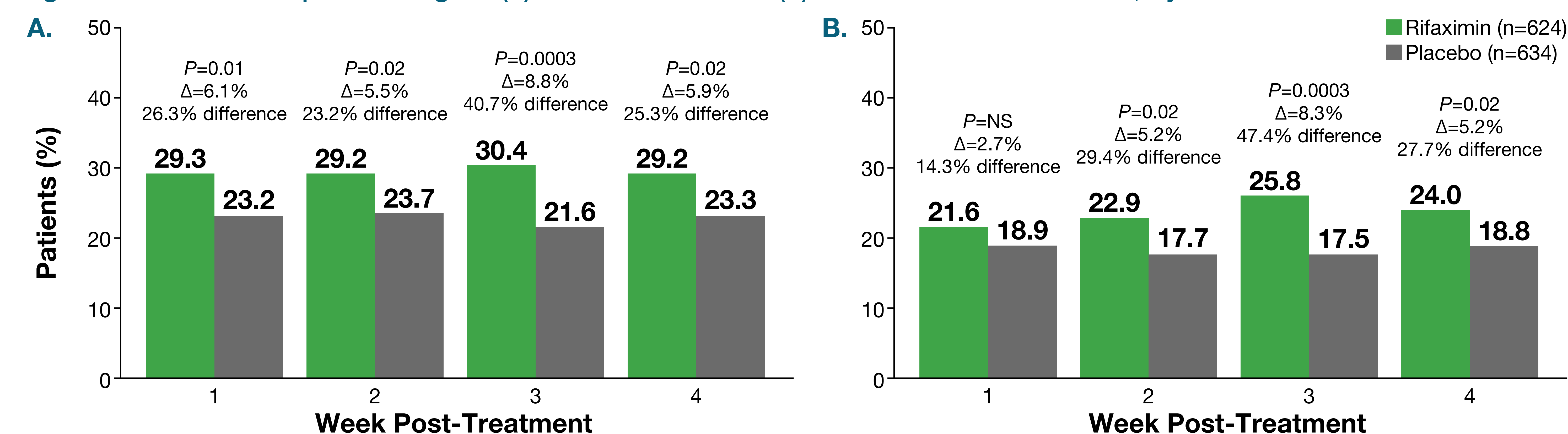
- As previously reported, a significantly greater percentage of patients treated with rifaximin had adequate relief of global IBS symptoms (patient response to: “In regard to all your symptoms of IBS, as compared with the way you felt before you started the study medication, have you, in the past 7 days,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



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

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



\*Response defined as  $\geq 30\%$  simultaneous improvement from baseline in weekly average pain score, weekly average bloating score, and percentage of days with bowel movement urgency. †Response defined as  $\geq 40\%$  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

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