POSTER NUMBER
Mo1291

Improvements in IBS-Related Quality of Life in a Randomized, Controlled Repeat Treatment Trial (TARGET 3) of Rifaximin for IBS-D

Brooks Cash, MD[1]; Anthony Lembo, MD[2]; Kavita Aggarwal, PharmD[3]; Enoch Bortey, PhD[3]; Craig Paterson, MD[3]; William P. Forbes, PharmD[3]
[1]University of South Alabama, Mobile, AL, USA; [2]Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]Salix Pharmaceuticals, Ltd., Raleigh, NC, USA

INTRODUCTION

- Irritable bowel syndrome (IBS) substantially impairs patient health-related quality of life (QOL) and social well-being[1,2]
- Patients with IBS have qualitative and quantitative alterations in the gut microbiota compared with healthy individuals[3-5]; therefore, targeting the gut microbiota for therapeutic intervention may be an effective option for diarrhea-predominant IBS (IBS-D)
- Rifaximin, an oral, minimally absorbed antimicrobial agent, significantly improved global and individual IBS-D symptoms in 2 randomized, placebo-controlled, phase 3 studies of single, short-course (2-week) therapy (TARGET 1 and 2)[6] and 1 randomized, placebo-controlled, phase 3 study of rifaximin repeat treatment (TARGET 3)[7]
- The impact of repeat treatment with rifaximin on QOL has not been previously reported

OBJECTIVE

- To assess the impact of repeat courses of rifaximin on IBS-related QOL

METHODS

Patient Population

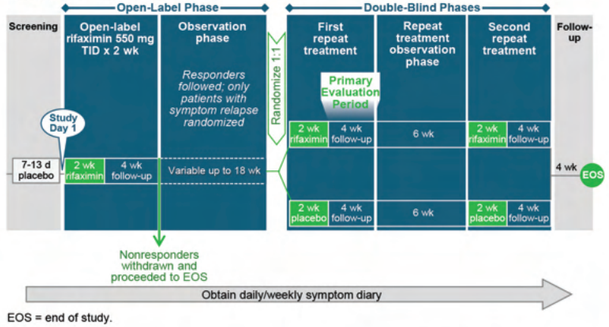
- Eligible adults were diagnosed with IBS-D (based on Rome III criteria) with average symptom severity scores during the screening phase of ≥3 for IBS-related abdominal pain (0 = no pain, 10 = worst possible pain you can imagine) and bloating (0 = not at all, 6 = a very great deal), with stools for ≥2 days per week meeting Bristol Stool Scale (BSS) criteria for type 6 (loose) or type 7 (watery) consistency
  - Exclusion criteria included a history of inflammatory bowel disease or having taken antidiarrheals, antispasmodics, narcotics, drugs indicated for IBS (eg, alosetron, lubiprostone), probiotics, or antibiotics within 14 days of study entry

Study Design

- Randomized, double-blind, phase 3, placebo-controlled, multicenter study
- After a 10-day placebo screening phase (Figure 1), patients meeting all eligibility criteria received open-label rifaximin 550 mg 3 times daily (TID) for 2 weeks, followed by a 4-week treatment-free follow-up period to assess response (defined as a patient meeting weekly response criteria for both abdominal pain [≥30% improvement from baseline in mean weekly pain score] and stool consistency [≥50% decrease from baseline in number of days/week with BSS type 6 or 7 stools] for ≥2 of 4 weeks during follow-up); nonresponders to open-label rifaximin were withdrawn from the study
  - Baseline data for the open-label phase were based on 7 days of patient diary data collected immediately preceding open-label rifaximin treatment
- Responders were subsequently followed, treatment free, for up to 18 additional weeks (observation phase) or until relapse (defined as loss of response for either abdominal pain or stool consistency for ≥3 out of a consecutive, rolling 4-week period during the 18-week observation phase)
- Patients who relapsed were randomly assigned (1:1) to receive two 2-week repeat treatment courses of rifaximin 550 mg TID or placebo, with repeat courses separated by 10 weeks
- Baseline data for the double-blind phase were based on 7 days of patient diary data collected immediately preceding repeat treatment

METHODS

Figure 1. Study Design



EOS = end of study.

Quality-of-Life Assessments

- QOL was assessed using a validated 34-item IBS-QOL questionnaire[8] with each item scored on a 5-point scale (1 = "not at all" to 5 = "extremely" or "a great deal"); data were converted via linear transformation to a summed score (range, 0–100), with higher score indicating better QOL
  - QOL was assessed for the overall score and for 8 subdomain scores
- IBS-QOL questionnaire was implemented at various timepoints at the clinic (eg, open-label baseline, double-blind baseline) or by phone (eg, end of 4-week open-label follow-up, last visit double-blind repeat treatment period)
- Change from open-label baseline to Week 4 of follow-up was analyzed using descriptive statistics; change from double-blind baseline to last visit and *P* values were analyzed using a general linear model with fixed effects for analysis center, treatment, and double-blind baseline scores; between-groups data were compared using least squares mean (LSM) differences

RESULTS

- A total of 2579 patients received open-label rifaximin (Table)
- At 4 weeks post-treatment, patients treated with open-label rifaximin reported improvements in IBS-QOL (Figure 2), with a mean improvement of 54.9% in overall IBS-QOL score (95% confidence interval, 48.4%–61.4%)
- In the double-blind treatment phases, 636 patients who initially responded to open-label rifaximin and relapsed received repeat treatment with rifaximin or placebo (Table)
- A significant improvement in overall IBS-QOL score from double-blind baseline to last visit was observed for repeat rifaximin versus placebo (LSM difference = 3.0; *P* = 0.049; Figure 3)

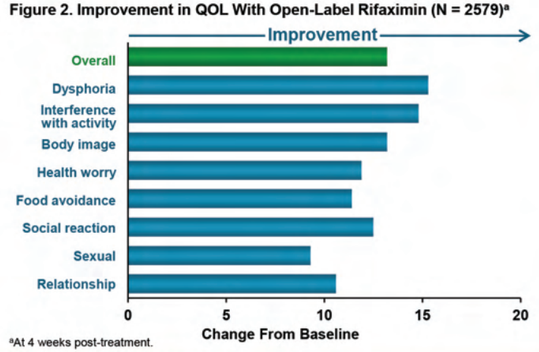
RESULTS

Table. Demographic and Baseline Characteristics

Characteristic		Open-Label Population: Rifaximin 550 mg TID (N = 2579)	Double-Blind Population: Rifaximin 550 mg TID (n = 328)	Double-Blind Population: Placebo (n = 308)
Age, y, mean (SD)		46.4 (13.7)	47.9 (14.2)	45.6 (13.8)
Sex, male:female, %		32:68	32:68	29:71
Race, n (%)	White	2155 (83.6)	273 (83.2)	262 (85.1)
	Black	289 (11.2)	37 (11.3)	31 (10.1)
	Other	135 (5.2)	18 (5.5)	15 (4.9)
Duration since first onset of IBS symptoms, y, mean (SD)		10.9 (10.8)	11.4 (11.0)	11.2 (10.9)
Number of daily bowel movements, mean (SD)		3.9 (2.2)	3.8 (2.1)	3.7 (2.1)
IBS-QOL overall score, n (%)	>40 (nonsevere)	1611 (62.5)	190 (61.7)	193 (58.8)
	≤40 (severe)	948 (36.8)	117 (38.0)	133 (40.5)
	Missing	20 (0.8)	1 (0.3)	2 (0.6)
Baseline IBS-QOL domain scores, mean (SD)	Overall	48.3 (21.2)	54.7 (23.5)[a]	55.0 (24.2)
	Dysphoria	48.7 (25.5)	57.8 (26.6)	57.8 (27.5)
	Interference with activity	39.5 (23.0)	46.3 (25.4)	46.8 (26.6)
	Body image	47.9 (24.1)	52.2 (26.3)	51.9 (26.3)
	Health worry	55.1 (21.9)	59.7 (23.3)	60.7 (24.4)
	Food avoidance	34.0 (27.0)	39.6 (28.5)	40.2 (29.0)
	Social reaction	52.6 (26.1)	58.1 (28.9)[a]	59.5 (27.5)
	Sexual	65.2 (32.0)	69.7 (31.8)	69.4 (33.5)
	Relationship	58.9 (26.5)	64.0 (27.2)[a]	64.2 (28.6)

[a]Data missing for 1 patient in rifaximin group.
SD = standard deviation.

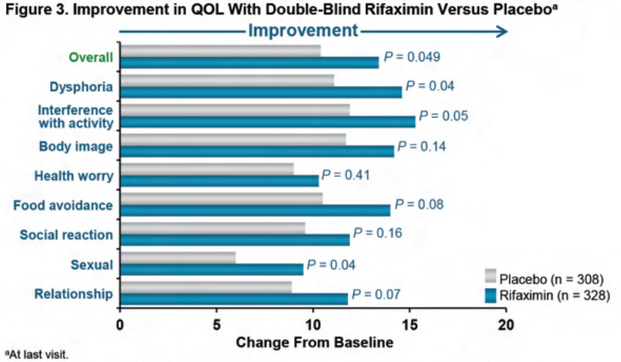
Figure 2. Improvement in QOL With Open-Label Rifaximin (N = 2579)[a]



[a]At 4 weeks post-treatment.

RESULTS

Figure 3. Improvement in QOL With Double-Blind Rifaximin Versus Placebo[a]



[a]At last visit.

- IBS-QOL scores were slightly higher prior to repeat treatment in patients treated with open-label rifaximin who experienced symptom recurrence (ie, higher QOL scores at double-blind baseline [Table])
- After 2 repeat courses, numeric between-group differences favoring rifaximin versus placebo were observed for IBS-QOL subdomains: dysphoria (Δ = 3.4; *P* = 0.04); interference with activity (Δ = 3.4; *P* = 0.05); body image (Δ = 2.5; *P* = 0.14); health worry (Δ = 1.3; *P* = 0.41); food avoidance (Δ = 3.4; *P* = 0.08); social reaction (Δ = 2.3; *P* = 0.16); sexual (Δ = 3.5; *P* = 0.04); and relationship (Δ = 2.9; *P* = 0.07)
  - Many of these between-group differences represented a 15% to 25% increase in QOL scores for repeat treatment with rifaximin versus placebo

CONCLUSION

- **In patients with IBS-D, repeat treatment with rifaximin provided incremental overall and subdomain QOL improvement in addition to the enduring improvement observed following initial treatment with open-label rifaximin**

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DISCLOSURES: BC has served as a consultant, advisory board member, or member of the speakers' bureau for Avantis Pharmaceuticals, Inc., IM Health, Ironwood Pharmaceuticals, Prometheus Laboratories, Inc., Salix Pharmaceuticals, Ltd., and Takeda Pharmaceuticals USA. AL has served as a consultant for Salix Pharmaceuticals, Ltd. KA, EB, CP are employees of Salix Pharmaceuticals, Ltd. WPF is an officer and employee of Salix Pharmaceuticals, Ltd.

ACKNOWLEDGEMENTS: The study was supported by Salix Pharmaceuticals, Ltd. Technical editorial and medical writing assistance was provided under the direction of the authors by Mary Beth Moncrief, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this support was provided by Salix Pharmaceuticals, Ltd.