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Enduring Effects Following a Course of Rifaximin Therapy in Patients With IBS-D: Incremental Benefit Upon Repeat Treatment

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INTRODUCTION

- Patients with irritable bowel syndrome (IBS) exhibit qualitative and quantitative alterations in their gut microbiota compared with healthy individuals;[1-3] therefore, targeting the gut microbiota may be an effective treatment for diarrhea-predominant IBS (IBS-D)
- Rifaximin, an oral, minimally absorbed antimicrobial agent, significantly improved global and individual IBS-D symptoms in two randomized, placebo-controlled, phase 3 studies of single, short-course (2-week) therapy (TARGET 1 and 2)[4]
- Repeat treatment with rifaximin has not been previously evaluated in a large, randomized, controlled study

OBJECTIVE

- To assess the profile of residual IBS symptom improvement in patients who initially responded to rifaximin, experienced symptom recurrence, and received repeat treatment with rifaximin in the TARGET 3 study

METHODS

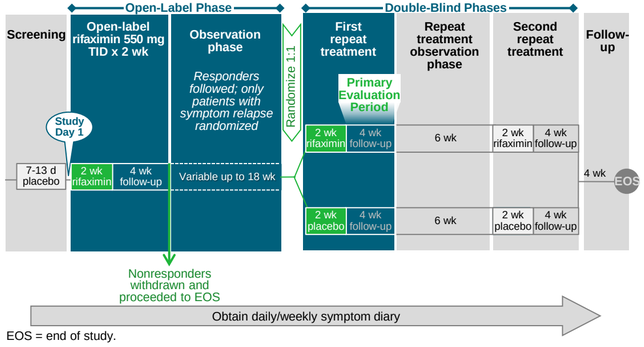
Patient Population

- Adults 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 (scale 0–10; 0 = no pain, 10 = worst possible pain you can imagine) and bloating (scale 0–6; 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, multinational study

Figure 1. Study Design



EOS = end of study.

METHODS

- After a 10-day placebo screening phase, 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 (Figure 1)
  - Baseline data for the open-label phase were based on 7 days of patient diary entries collected immediately preceding open-label rifaximin treatment
  - A responder was 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
- Responders were subsequently followed, treatment free, until relapse or for up to 18 additional weeks (observation phase)
  - Relapse was 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 then randomly assigned (1:1) to receive repeat treatment with rifaximin 550 mg TID or placebo for 2 weeks followed by a 4-week, treatment-free follow-up period to assess response (primary evaluation period; Figure 1)
  - Baseline data for the double-blind phase were based on 7 days of patient diary entries collected immediately preceding repeat treatment
- Efficacy assessments included:
  - US Food and Drug Administration composite endpoint after first repeat treatment (primary endpoint): weekly responder for both IBS-related abdominal pain (≥30% improvement from baseline) and stool consistency (≥50% decrease from baseline in frequency of type 6 or 7 stools) during ≥2 weeks of the 4-week follow-up period
  - IBS-related bloating (key secondary endpoint): “In regards to your specific IBS symptom of bloating, on a scale of 0–6, how bothersome was your IBS-related bloating in the last 24 hours?” (0 = not at all, 6 = a very great deal)
  - Fecal urgency (secondary endpoint): “Have you felt or experienced a sense of urgency in the last 24 hours with any of your bowel movements?” (Yes/No)
  - Global IBS symptoms (secondary endpoint): “How bothersome were your symptoms of IBS in the last 24 hours?” (7-point scale; 0 = not at all, 6 = a very great deal)

RESULTS

- 636 (59.2%) of 1074 patients who initially responded to open-label rifaximin and subsequently relapsed were included in the double-blind phase and received repeat treatment with rifaximin or placebo (Table)
- Symptom severity did not return to baseline levels after patients, who initially responded to open-label rifaximin, met predefined criteria for relapse
  - At the time of double-blind randomization, baseline scores for all IBS-related symptoms for the 636 patients were significantly lower compared with baseline scores at the beginning of open-label rifaximin treatment ($P < 0.0001$ for all; paired t-test; Figure 2)
  - Symptom severity at time of recurrence indicated that the 636 patients who met the criteria for relapse were still experiencing an ~20% improvement in abdominal pain score and ~14% improvement in days per week with loose or watery stool relative to their open-label baseline results
    - Similar degree of carryover effects were observed with other IBS symptoms
- Repeat treatment with rifaximin provided significant incremental benefit (Δ=8%) versus placebo ($P = 0.02$; Figure 3)

RESULTS

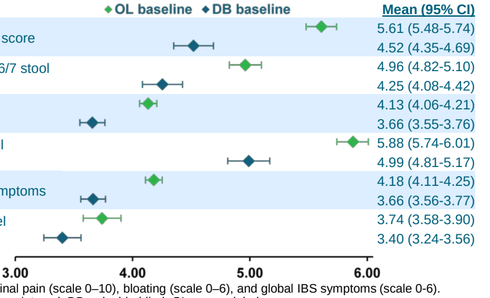
Table. Demographic and Baseline Characteristics

Characteristic	Double-Blind Population: Rifaximin 550 mg TID (n = 328)	Double-Blind Population: Placebo (n = 308)
Age, y, mean (SD)	47.9 (14.2)	45.6 (13.8)
Sex, n (%)		
Male	106 (32.3)	89 (28.9)
Female	222 (67.7)	219 (71.1)
Race, n (%)		
White	273 (83.2)	262 (85.1)
Black	37 (11.3)	31 (10.1)
Other	18 (5.5)	15 (4.9)
Duration since first onset of IBS symptoms, y, mean (SD)	11.4 (11.0)	11.2 (10.9)
Daily symptom score, mean (SD)[a]		
Abdominal pain	5.7 (1.7)	5.5 (1.6)
Stool consistency	5.6 (0.8)	5.6 (0.8)
Bloating	4.2 (0.9)	4.1 (0.9)
Global IBS symptoms	4.2 (0.9)	4.1 (0.9)
Number of daily bowel movements, mean (SD)	3.8 (2.1)	3.7 (2.1)
Days per week with stool type 6 or 7, mean (SD)	4.9 (1.8)	5.0 (1.7)
Days per week with stool urgency, mean (SD)	5.9 (1.7)	5.8 (1.7)

[a]Scale score ranges: abdominal pain (scale 0–10), bloating (scale 0–6), stool consistency (scale 1-7), and global IBS symptoms (scale 0-6).
SD = standard deviation.

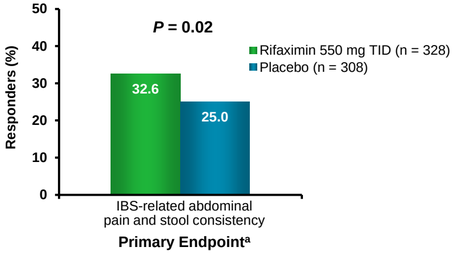
RESULTS

Figure 2. IBS Symptoms[a] at Open-Label Baseline and Repeat Treatment Baseline (n = 636)



[a]Scale score ranges: abdominal pain (scale 0–10), bloating (scale 0–6), and global IBS symptoms (scale 0-6).
Avg = average; CI = confidence interval; DB = double-blind; OL = open-label.

Figure 3. Response to Repeat Rifaximin Treatment



[a]Missing data were handled using “worst case” analysis method: patients who reported <4 days of diary data in a given week were considered nonresponders for that week.

CONCLUSIONS

- **Patients with IBS-D experienced persistent symptom improvement after a single, 2-week course of rifaximin therapy**
- **In patients who relapsed, IBS symptom severity at time of repeat treatment was substantially lower than that observed at open-label baseline**
- **Repeat treatment with rifaximin in patients meeting criteria for IBS relapse provided benefit to the enduring symptom improvements following initial treatment**

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