POSTER NUMBER

Su1195

Rifaximin Repeat Treatment for Diarrhea-Predominant Irritable Bowel Syndrome and Impact on *Clostridium Difficile* Infection Development

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INTRODUCTION

- Rifaximin, a nonsystemic antibiotic, has been available for >30 years (Italy since 1987; United States since 2004) and is currently marketed in at least 47 countries
- In the United States, rifaximin 550 mg tablets is indicated for the treatment of irritable bowel syndrome (IBS) with diarrhea in adults and for the reduction in risk of overt hepatic encephalopathy recurrence in adults[1]
  - Phase 3 randomized, double-blind (DB), placebo-controlled trials have demonstrated the efficacy and safety of single[2] and repeated courses[3] of rifaximin in the treatment of diarrhea-predominant IBS (IBS-D)
  - In patients with cirrhosis and recurrent hepatic encephalopathy, long-term (ie, ≥2 years) daily treatment with rifaximin was safe and well tolerated[4]
- Antibiotic use is considered a major risk factor for *Clostridium difficile* infection[5]
  - The systemic antibiotics ampicillin, amoxicillin, cephalosporins, clindamycin, and fluoroquinolones are most frequently associated with *C difficile* infection; overall, most systemic agents carry at least some risk, even if uncommonly observed[5]

AIM

- To determine the potential impact of treatment with the nonsystemic antibiotic rifaximin on the development of *C difficile* infection in adults with IBS-D

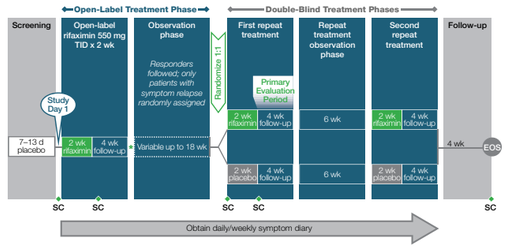
METHODS

Study Design and Patient Population

- Phase 3, randomized, DB, placebo-controlled, 51-week study (**Figure**)
- Adults with IBS-D (Rome III criteria), daily abdominal pain score ≥3 (scale range, 0-10), bloating score ≥3 (scale range, 0-6), and ≥2 days/week Bristol Stool Scale type 6/7 stool received open-label (OL) rifaximin 550 mg three times daily (TID) for 2 weeks, followed by a 4-week treatment-free period to assess response
- Responders were followed for an additional 18 weeks, or until symptom recurrence; patients with recurrence were randomly assigned to receive 2 repeat courses of DB rifaximin 550 mg TID or placebo for 2 weeks; each course separated by 10 weeks

METHODS

Figure. Study Design



*Nonresponders withdrawn and proceeded to EOS.
EOS = end of study; SC = stool sample collection; TID = three times daily.
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C difficile Testing

- Stool samples were collected before (OL baseline) and after OL rifaximin treatment, before (DB baseline) and after the first DB treatment, and at end of study (**Figure**)
- At OL baseline, stool samples were collected and tested for Toxins A and B using enzyme immunoassay (EIA) (Wampole®)
  - Patients were confirmed to be negative for Toxins A and B in order to remain in the study
- Stool samples were collected and tested for *C difficile* Toxin B gene (tcdB) using real-time polymerase chain reaction (PCR) for any patient suspected of having *C difficile* colitis
  - Worsening acute diarrhea and abdominal pain at any point during the study and defined by: ≥3 loose or watery stools during previous 24 hours and ≥1 other sign of enteric infection (eg, fever, nausea/loss of appetite, vomiting, worsening severe abdominal pain) during the study
- For any stool sample testing positive for *C difficile*, additional confirmatory PCR testing was performed for the Toxin B gene
- A positive *C difficile* test was recorded as an adverse event and the patient was to be withdrawn from the study

RESULTS

- Among the 2579 patients with IBS-D who received OL rifaximin 550 mg TID (**Table 1**), 2357 patients with baseline EIA data at the start of the OL phase

RESULTS

Table 1. Patient 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)
Female, n (%)	1760 (68.2)	222 (67.7)	219 (71.1)
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)
Average daily score, mean (SD)			
Abdominal pain	5.5 (1.7)	5.7 (1.7)	5.5 (1.6)
Stool consistency	5.6 (0.8)	5.6 (0.8)	5.6 (0.8)
Bloating	4.1 (0.9)	4.2 (0.9)	4.1 (0.9)
IBS symptoms	4.2 (0.9)	4.2 (0.9)	4.1 (0.9)
Number of daily bowel movements, mean (SD)	3.9 (2.2)	3.8 (2.1)	3.7 (2.1)
Days with BSS type 6/7 stool in a week, d, mean (SD)	4.9 (1.8)	4.9 (1.8)	5.0 (1.7)

BSS = Bristol Stool Scale; IBS = irritable bowel syndrome; SD = standard deviation; TID = three times daily.
*At enrollment.
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Open-Label Phase

- Thirty-seven (1.6%) of 2357 patients with baseline EIA data at the start of the OL phase were withdrawn due to a positive EIA test, per protocol
- 3 patients who did not have stool samples tested prior to first OL rifaximin dose (ie, did not follow protocol) had a positive test after beginning treatment
  - Stool samples were positive on last day of OL rifaximin treatment and 1 and 25 days post OL rifaximin, respectively
  - None of the 3 patients reported symptoms suggestive of active *C difficile* infection and may have been asymptomatic carriers; none entered the DB phase of the study

Double-Blind Phase

- No positive EIA tests for *C difficile* were reported at DB baseline or after completion of first DB treatment
- One patient (67-year-old female) in the DB rifaximin group developed *C difficile* infection 37 days after completing the first repeat treatment course (**Table 2**)
  - The investigator believed that this infection was not considered to be related to rifaximin but rather related to the systemic cephalosporin antibiotic cefdinir taken for a urinary tract infection

Table 2. Patient Narrative

- Negative for *C difficile* Toxins A and B by EIA at OL baseline
- Concomitant medications included esomeprazole magnesium for GERD
- Treated with OL rifaximin 550 mg TID for 2 weeks and 1 repeat treatment course of DB rifaximin 550 mg TID
- 22 days after completing DB rifaximin treatment, the patient began a 10-day course of cefdinir for a UTI
- 32 days after completing DB rifaximin, the patient finished the 10-day course of cefdinir
- After completing the cefdinir course, the patient developed severe diarrhea, dehydration, lower abdominal cramping, and weakness
  - Diarrhea had started 4 days prior
- Patient presented to the ED and noted a previous history of *C difficile* colitis ~9 months before study
- A CT scan of the abdomen and pelvis revealed bowel wall thickening of the entire colon with mild pericolonic increased fat density, which suggested inflammation
- 37 days after rifaximin DB treatment, a stool sample was positive for *C difficile*
- The infection was treated with 4 weeks of oral vancomycin and the infection resolved; the patient discontinued further study participation

CT = computed tomography; DB = double-blind; EIA = enzyme immunoassay; GERD = gastroesophageal reflux disease; ED = emergency department; OL = open-label; TID = three times daily; UTI = urinary tract infection.

CONCLUSIONS

- **Repeat treatment with rifaximin did not predispose patients to infection with *C difficile*, a finding that is consistent with the well-established safety profile for rifaximin**

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

DISCLOSURES: MP reports serving as a consultant for and receiving research grants from Salix Pharmaceuticals. Additionally, Cedars-Sinai Medical Center has a licensing agreement with Salix Pharmaceuticals. PS and BC report serving as consultants for Salix Pharmaceuticals. ZH reports being an employee of Salix Pharmaceuticals.

Research funded by: Salix Pharmaceuticals