XIFAXAN® (rifaximin) Tablets, 550 mg
NDA 21-361

Briefing Document for Gastrointestinal Drugs Advisory Committee Meeting
16 November 2011

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1. Executive Summary

This briefing document is prepared by Salix Pharmaceuticals, Inc. (Salix) for the Gastrointestinal Drugs Advisory Committee (GIDAC) meeting on November 16, 2011. The committee has been convened in order to discuss the design of a clinical trial to evaluate the safety, efficacy and durability of response with repeat treatment cycles of XIFAXAN® (rifaximin) for non-constipation irritable bowel syndrome (non-C IBS). This document provides relevant information regarding IBS and the medical need for effective therapies, the clinical development program and results-to-date for rifaximin in the treatment of non-C IBS, and a proposed study design to evaluate the efficacy and safety of repeat rifaximin treatment in the non-C IBS population.

1.1. IBS and Unmet Medical Need

Irritable bowel syndrome is a heterogeneous gastrointestinal (GI) disorder characterized by frequent and often debilitating symptoms (e.g., diarrhea, bloating, abdominal pain, urgency to defecate, gas, fecal incontinence).[1,2,3,4,5] Patients suffering with IBS often present with variable symptomatology and fluctuate between symptomatic and non-symptomatic periods.[6,7] IBS causes substantial impairment in health-related quality of life, loss of work and productivity, social embarrassment and high health care costs.[4,5] The prevalence of IBS is believed to be 10 to 15% of the United States (US) population; however, only 15% of IBS patients actually seek medical treatment, which may be due in part to the lack of effective therapies.[1,7,8,9,10,11,12]

At present the diagnosis of IBS is based on characteristic patient-reported symptoms that occur in the absence of an identifiable anatomical or metabolic cause. The diagnosis and subtyping of IBS have been standardized using symptom-based criteria (e.g., Manning and subsequently the Rome criteria). Patients are generally subtyped as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or IBS with an alternating stool pattern between diarrhea and constipation (i.e., mixed IBS or alternating IBS), with each comprising approximately one-third of the IBS population. In the rifaximin clinical development program patients with IBS-C were excluded, and the population studied is referred to as non-C IBS (i.e, IBS patients presenting with diarrhea).

Despite the tremendous burden of IBS, there remains a significant unmet need for effective and safe therapies, particularly for non-C IBS. There is only one approved drug for IBS patients presenting with diarrhea, Lotronex® (alosetron). This drug requires dosing on a chronic daily basis and is only available through a restricted access program to females with severe IBS-D.[13,14,15,16]

1.2. Developing Therapies for IBS

The underlying etiology and pathophysiology behind IBS are not well understood but likely involve the interplay of several factors. IBS has been characterized as a disorder involving an altered brain-gut axis that can be associated with GI hypersensitivity and GI motor dysfunction.[17,18,19] More recently, alterations in the intestinal microbiota, pathogenic bacterial infection, genetic pre-determinants, altered gut immune function, and inflammation have emerged as possible contributing etiologies.[20,21,22,23,24]

Because IBS is considered a heterogeneous condition with no reliable biomarkers, drug development has been challenging, typically rendering a specific product useful in some but not all patients.

Mainstays of treatment have targeted the symptoms of IBS and included antidiarrheals, antiflatulents, stool bulking agents, and antispasmodics. In the 1990s drug development focused on altering GI motility through serotonin receptor agonism or antagonism to provide relief from IBS symptoms.[13,25] Unfortunately, symptoms were noted to return almost immediately upon drug discontinuation. Thus, these products required chronic daily use to provide sustained relief. More recently, a focus has been alteration of the host-microbiome interactions through use of antibiotics or probiotics.

The equilibrium of the gut microbiome has been shown to have a significant influence on human health and disturbances can adversely affect essential GI functions.[26,27] Enteric bacterial dysbiosis is best viewed as an altered microbial ecosystem and not an infection *per se*. Several lines of evidence demonstrate a role for quantitative and/or qualitative imbalances in the GI microbiota of IBS patients, including a correlation between IBS and prior GI infections, a correlation between IBS symptoms and bacterial overgrowth in the small intestine, and studies linking IBS symptoms to subtle changes in the gut flora or to altered gut flora leading to immune activation and inflammation in the colonic mucosa.[28,29,30,31,32,33,34,35,36,37] The development of rifaximin for IBS has focused on the theory that the symptoms of IBS in some patients are due to enteric bacterial dysbiosis, abnormal colonization of the gut, and/or interactions between the gut microbiome and the host.[19,38,39,40,41,42]

Although multiple lines of evidence support a bacterial hypothesis for the etiology of IBS, the challenge of diagnosis is multifaceted. Because no sufficiently sensitive and specific biomarker has been identified, the diagnosis of IBS currently is symptom-based. The reputed gold standard for diagnosis of bacterial overgrowth in IBS is jejunal aspirate culture, but this test is highly invasive and difficult to perform.[43,44] Indirect lactulose or glucose breath testing is designed to serve as a surrogate measure of bacterial overgrowth by measuring bacterial metabolism products non-invasively.[43,44,45] While breath testing is a controversial diagnostic tool due to questions of sensitivity and specificity, it may ultimately provide useful diagnostic or prognostic information, but requires further investigation.

1.3. Regulatory History of Rifaximin in IBS

Rifaximin is approved in 36 countries for various indications (e.g., intestinal infection, travelers' diarrhea [TD], hepatic encephalopathy [HE], IBS, uncomplicated diverticulitis, small-intestinal bacterial overgrowth [SIBO], prophylaxis of infective complications). With considerable post-marketing worldwide exposure (20+ years) rifaximin has not been associated with known major safety issues, and has never been withdrawn from the market for safety reasons.

In the US, rifaximin 200 mg tablets (XIFAXAN®) were approved in 2004 for the treatment of TD caused by noninvasive strains of *Escherichia coli (E. coli)* (200 mg three times daily [TID] for 3 days). In 2010, rifaximin 550 mg tablets (XIFAXAN®) were approved for the reduction in risk of overt HE recurrence (550 mg twice daily [BID] as chronic therapy). Since the first two US approvals there have been no notable changes in labeling based on product use.

In the development of rifaximin for non-C IBS (550 mg TID for 14 days), Salix has worked closely with the Food and Drug Administration (FDA), as well as key thought leaders, to design and conduct confirmatory clinical trials. This completed clinical program, including 2 large, adequate and well controlled phase 3 trials (TARGET 1 [RFIB3007] and TARGET 2 [RFIB3008]) and a dose ranging phase 2b study (RFIB2001), demonstrated rapid and persistent relief from IBS symptoms following a single 2-week course of therapy.[46] These trials have

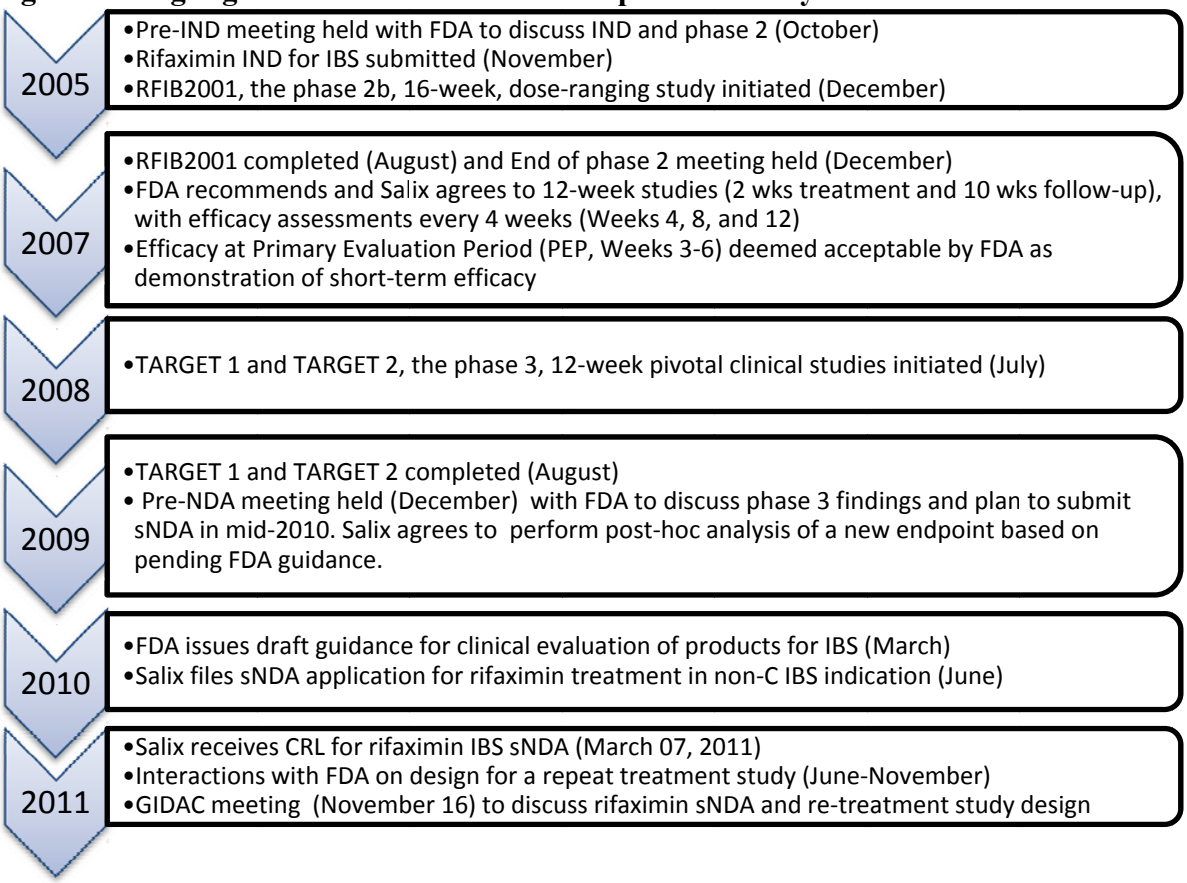
shown a positive benefit/risk ratio, with an adverse event (AE) profile comparable to placebo with one course of treatment.

Salix submitted a supplemental new drug application (sNDA) in June 2010 with the following proposed indication statement: "The treatment of non-C IBS and IBS-related bloating in patients ≥ 18 years of age." The recommended dose of rifaximin for non-C IBS was 550 mg taken orally TID for 14 days. On March 7, 2011 the FDA issued a Complete Response Letter (CRL) indicating that the sNDA could not be approved in its present form. In the CRL, the FDA requested prospective clinical evidence that rifaximin is effective with repeat treatment following the recurrence of symptoms in patients who respond to an initial course of rifaximin.

Since the CRL, Salix has worked collaboratively with the FDA to discuss appropriate study design elements for a repeat treatment (i.e., re-treatment) protocol. Based on these interactions, Salix has developed a study proposal for discussion during this GIDAC meeting. While retrospective uncontrolled data are available for repeat use of rifaximin in IBS, this proposal is intended to add prospective controlled data.

A summary of key milestones in the rifaximin IBS development program is presented in Figure 1.

Figure 1 Highlights of Rifaximin IBS Development History



Abbreviations: IND = Investigational New Drug Application; IBS = irritable bowel syndrome; sNDA = supplemental New Drug Application; non-C IBS = non-constipation IBS; GIDAC = Gastrointestinal Drugs Advisory Committee; and HE = hepatic encephalopathy.

1.4. Rifaximin Pharmacology

Rifaximin is a well characterized drug and has demonstrated a beneficial treatment effect in a variety of conditions including TD, HE, Crohn's disease, ulcerative colitis, uncomplicated diverticulitis, and IBS, in which the interaction between gut bacterial metabolic products and host GI mucosa has been implicated in disease etiology.

Rifaximin is the first drug for IBS with persistent efficacy following a short course of treatment. The precise mechanism by which rifaximin exerts this beneficial effect in IBS is unknown; however, based on current in vitro and in vivo data there are three plausible explanations for rifaximin's clinical efficacy in IBS:

- Rifaximin affects gut bacteria and reduces bacterial products that negatively affect the host;
- Rifaximin induces intestinal detoxification and decreases inflammatory response mechanisms of the host to bacterial products; and
- Rifaximin impacts both the bacterial and host response and the bacteria-host interface.

Rifaximin In Vitro and In Vivo Effects: Rifaximin binds to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.[47] In vitro, rifaximin has a broad spectrum of activity against both aerobic and anaerobic Gram-positive and Gram-negative organisms.[48,49,50] Despite the in vitro activity, rifaximin administration in vivo is not associated with eradication of beneficial gut flora.[51] Both in vitro and in vivo data demonstrate that rifaximin is associated with multiple mechanisms which are not generally ascribed to antibiotics. These mechanisms include alterations in bacterial response and signaling, host detoxification and inflammatory response, and host-bacteria interactions.

Production of virulence factors and metabolic products by enteric bacteria are inhibited at sub-inhibitory rifaximin concentrations.[52,53] In vitro incubations of human fecal microbiota have shown rifaximin-induced increases in populations of bacterial strains believed to be beneficial to gut homeostasis, and increases in short-chain fatty acids believed to benefit GI mucosa.[54]

Effects of rifaximin on the interaction between GI bacteria and host cells have been documented; the adhesion of enteroaggregative *E. coli* (EAEC) to human epithelial cells in vitro was reduced significantly when epithelial cells were pretreated with rifaximin as compared with control cells or other antibiotics.[55] Rifaximin also has been shown to inhibit inflammatory cytokine release in human HEp-2 cells, an effect that may be related to its effects on GI lumen-localized pregnane X receptor (PXR) mediated host detoxification mechanisms.[56,57]

Rifaximin has been shown to activate PXR, resulting in increased expression of PXR target genes in the intestine;[58] P-glycoprotein and CYP3A4 mRNA were increased by 9- and 20-fold, respectively, upon incubation with rifaximin in an in vitro model.[59] These target genes serve as human enteric defense mechanisms against harmful bacterial metabolic products, and their increased expression in the GI tract in the presence of rifaximin may result in an enhanced host defense against GI dysbiosis. Across multiple studies and populations, data indicate a relationship between gene variants in PXR and inflammatory bowel disease pathogenesis.[60,61,62] Rifaximin-induced activation of intestinal PXR may also have a therapeutic effect on IBS.

Clinical Pharmacology: Rifaximin's minimal oral systemic availability is consistent with its low intestinal permeability and low aqueous solubility; its systemic absorption is limited further by efflux transport by intestinal P-glycoprotein (P-gp). In adults, rifaximin 800 mg/day for

3 days resulted in concentrations of about 8000 µg/g in stools.[63] Human and animal studies demonstrate that a small fraction of absorbed rifaximin is excreted in bile.

Systemic exposure of rifaximin following oral administration is minimal in all populations studied to date, including IBS. Following repeat dosing of rifaximin 550 mg TID, mean steady-state AUC_{tau} was 16.0 ng·h/mL and mean steady-state maximum concentration (C_{max}) was 4.22 ng/mL in IBS patients, consistent with concentrations observed in healthy volunteers.[64,65]

In vitro, rifaximin does not inhibit human hepatic cytochrome P450 (CYP) isoenzymes significantly.[66] In vitro, rifaximin induces CYP3A4 and P-glycoprotein expression to a limited extent, consistent with PXR activation.[59,67] In two drug-drug interaction studies conducted in healthy volunteers, rifaximin (550 mg TID) did not affect the pharmacokinetics of either midazolam or the components of an oral contraceptive to a clinically significant extent. Based on the results of these drug interaction studies, no dose adjustment is required when co-administering rifaximin with other drugs.[68,69,70]

Rifaximin is gut-targeted and has negligible systemic exposure with plasma concentrations 2 to 3 orders of magnitude below that of other antibiotics, including those considered "non-systemic." The low systemic exposure of rifaximin results in lower selective pressure for development of extra-intestinal bacterial resistance, and rifaximin does not appear to cause the drastic alterations in beneficial GI microbiota associated with antibiotics used for systemic infection.[71,72,73]

Pharmacodynamics: Across two studies, rifaximin has demonstrated statistically significant efficacy and approximately linear dose response in eradicating SIBO as reflected by glucose breath test results.[74,75] Glucose breath test normalization rates for rifaximin doses of 600, 800, 1200, and 1600 mg/day were 17%, 27%, 60%, and 80%, respectively.[74,75] The maximum response was observed with a 1600 mg daily dose, similar to the dose tested in TARGET 1 and TARGET 2 (1650 mg daily dose).

1.5. Clinical Efficacy

The clinical efficacy of rifaximin in the treatment of non-C IBS is supported by the totality of evidence from clinical studies in phase 1, 2, and 3 and several published reports.[39,46,76,77] The primary clinical efficacy data comes from 2 pivotal, identically-designed, double-blind, placebo-controlled, phase 3 studies (TARGET 1 [RFIB3007] and TARGET 2 [RFIB3008]). Full results of the TARGET studies have been disclosed previously in a peer-reviewed scientific journal.[46] The data used to arrive at the rifaximin 550 mg TID dose and dosing regimen in phase 3 are described in detail in Section 4.3.7.

In the TARGET studies, subjects with IBS confirmed using the validated Rome II criteria were randomized 1:1 to rifaximin 550 mg TID or placebo for 14 days. TARGET 1 enrolled 623 patients (rifaximin: 309; placebo: 314) and TARGET 2 enrolled 635 patients (rifaximin: 315; placebo: 320). Subjects had characteristics of IBS-D without constipation at baseline, and were therefore considered to have had non-C IBS.

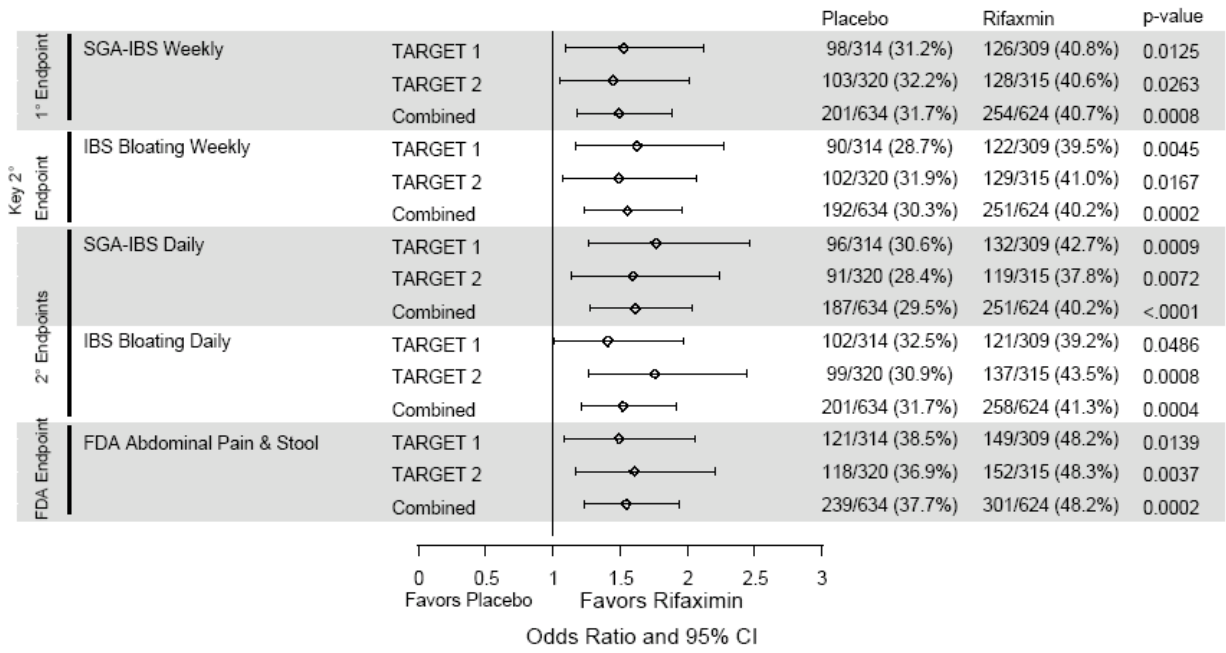
Rifaximin demonstrated efficacy in the treatment of non-C IBS based on statistically significant symptom relief versus placebo for the primary endpoint, which was defined as adequate relief in the primary evaluation period (PEP: Weeks 3-6):

- **Primary Endpoint:** TARGET 1 and TARGET 2 each met the pre-specified primary endpoint. Significantly more rifaximin patients had adequate relief of their global IBS

symptoms over the 1 month following treatment based on weekly subject global assessments (SGA); (TARGET 1: 41% vs. 31%, p = 0.0125; TARGET 2: 41% vs. 32%, p = 0.0263; Figure 2). This effect size was clinically meaningful (see Section 6.6).

- **Key Secondary Endpoint:** Significantly more rifaximin patients had adequate relief of their IBS-related bloating over the 1 month following treatment based on weekly SGA; (TARGET 1: 40% vs. 29%, p = 0.0045; TARGET 2: 41% vs. 32%, p = 0.0167; Figure 2).
- **FDA Draft Guidance Endpoint:** Significantly more rifaximin patients were responders in each trial for abdominal pain AND stool consistency (TARGET 1: 48% vs. 39%, p = 0.0139; TARGET 2: 48% vs. 37%, p = 0.0037; Figure 2).
- **Additional Secondary Endpoints:** Consistency of results was reflected in daily ratings of global IBS symptoms and IBS bloating (Figure 2).

Figure 2 Impact of Rifaximin on Relief of IBS Symptoms During the PEP (Weeks 3-6)



Source: TARGET 1 & 2 study data. This figure shows the percentage of responders by treatment group, and odds ratios for the likelihood of being a responder for the key study endpoints in the PEP (Weeks 3-6). P-values and odds ratio were obtained using the logistic regression model with fixed effects for treatment arm, analysis center, and study (combined data only).

Predefined and FDA-requested supplementary analyses were conducted in the TARGET studies to evaluate efficacy every 4 weeks (Weeks 4, 8, and 12). These analyses demonstrated that therapeutic benefit of rifaximin in non-C IBS patients was observed early in the TARGET studies and sustained over the 12 weeks of subject observation:

- Cumulative response analyses showed that the onset of the rifaximin treatment effect was rapid (observed within the 2-week treatment period) in the TARGET studies.
- Point prevalence findings (i.e., efficacy measured at each month), demonstrated that rifaximin subjects were consistently more likely to experience adequate relief of global IBS symptoms every 4 weeks over the entire 12 weeks.
- Rifaximin subjects were significantly more likely to experience persistent efficacy as

measured by number of months with relief during the entire 3 months and a more stringent definition of a responder for all 3 months.

- Degree of improvement in daily symptom scores demonstrate that rifaximin subjects experienced less bloating, less abdominal pain, better stool consistency, and reduced sense of urgency over 12 weeks compared with placebo.

Efficacy was robustly demonstrated in the TARGET studies in the PEP for the primary endpoint, key secondary endpoint, and FDA guidance endpoint with a single course of therapy. Other secondary endpoints demonstrated a consistent treatment effect. These findings confirm results from the 680-patient phase 2b study, RFIB2001, and placebo-controlled studies from the published literature demonstrating rifaximin to be effective in improving IBS symptoms, with a treatment effect which persists after cessation of therapy.[39,76,77]

1.6. Clinical Safety

The safety of rifaximin has been established through experience in multiple clinical studies in IBS and other indications with 5417 subjects, as well as extensive worldwide post-marketing exposure (20+ years). Salix-sponsored rifaximin studies have included IBS subjects (N=1930), HE subjects (N=719), TD subjects (N=2230), and healthy volunteers in clinical pharmacology trials (N=261). Analysis of the rifaximin safety database supports the safety of rifaximin in the non-C IBS patient population.

An overview of safety results from the TARGET studies is presented in Table 1.

Table 1 Overview of Safety Results from TARGET 1 and 2 (Combined Data Over 12 Weeks)

	Rifaximin 550 mg TID (n=624) n (%)	**Placebo (n=634)** n (%)
Any AEs	340 (54.5)	337 (53.2)
SAEs	10 (1.6)	15 (2.4)
AEs Resulting in Discontinuation	8 (1.3)	8 (1.3)
Deaths	0	0

Abbreviations: AE = adverse event, and SAE = serious adverse event.

- The overall safety profile during and following treatment with rifaximin was comparable to placebo.
- The most common AEs for rifaximin-treated subjects were headache (rifaximin 5%, placebo 6%), nausea (4%, 4%), diarrhea (3%, 3%), and urinary tract infection (3%, 2%).
- Serious adverse events (SAEs) were experienced in 1.6% of rifaximin and 2.4% of placebo subjects, with no reports of SAEs involving constipation, ischemic colitis, or death.
- There was no indication of clinically significant bacterial resistance. There were no treatment-emergent cases of *Clostridium difficile (C. difficile)* infection in the IBS program.
- There were no notable safety issues identified in clinical laboratory, vital signs, or concomitant medication data.

As further evidence of rifaximin's safety, HE patients with advanced liver disease using long-term (2-3 years) daily dosing demonstrated no increased risk of infection, with decreases in morbidity and hospitalizations. [78]

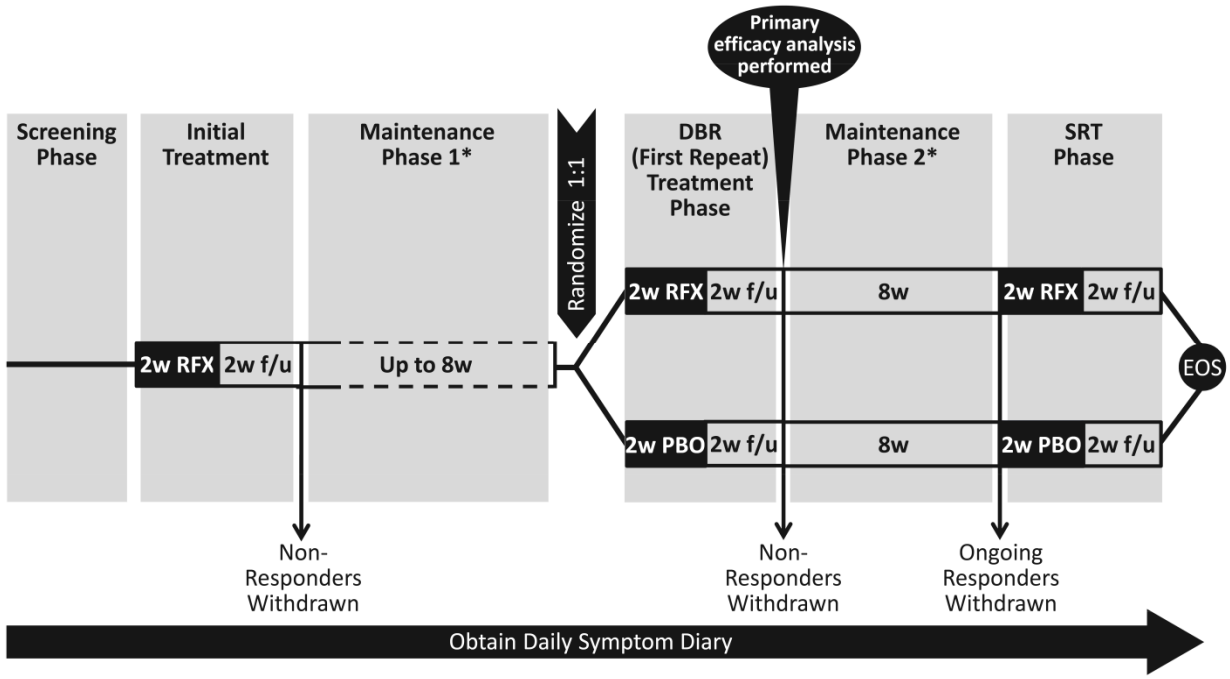
In a recent retrospective study presented at American Association for the Study of Liver Diseases (AASLD) 2011 examining the incidence of *C. difficile* infection in cirrhotic patients, patients taking rifaximin treatment had a significantly lower incidence of *C. difficile* associated diarrhea than those taking lactulose ($p < 0.007$).[79] In results presented at AASLD 2011 from a second retrospective study, rates of antibiotic-resistant infection in hospitalized cirrhotic patients were studied. Compared with an odds ratio of 1 for patients with no antibiotic exposure in the prior 30 days, patients receiving a systemic antibiotic had an odds ratio of 4.8 (95% CI: 1.5 – 15.4) compared with patients receiving a non-systemic antibiotic (primarily rifaximin), with an odds ratio of 0.48 (95% CI: 0.12 – 2.01). The data indicate that recent exposure to systemic, but *not* non-systemic, antibiotics was the primary predictor of the development of antibiotic-resistant infection.[80]

1.7. Rifaximin Repeat Treatment Study Proposal

Rifaximin provides benefits for IBS patients with persistent relief following a single 2-week regimen. The FDA has requested evidence that rifaximin is effective with repeat treatment following recrudescence of symptoms. At present, data from multiple retrospective chart reviews in the literature suggest that rifaximin patients who develop a recurrence of IBS symptoms are being successfully re-treated by their physicians in the clinical setting (Section 8.2). Results of these chart reviews demonstrate a high probability of success with repeat use.[81,82,83,84] The proposed study is a multi-center, randomized, double-blind, placebo-controlled trial with non-C IBS patients designed to demonstrate efficacy and safety of rifaximin on repeat treatment (Figure 3).

The **Primary Endpoint** is the proportion of subjects who are responders to repeat treatment in both IBS-related abdominal pain AND stool consistency during the 2 weeks treatment; 2-week treatment-free follow-up, an endpoint consistent with recommendations for IBS in the FDA draft guidance.[85] **Response** in the study is defined as subjects who experience treatment success for IBS-related abdominal pain AND stool consistency for at least 2 out of 4 weeks during a 4-week assessment period. A subject will be considered to have met **Recurrence** criteria when treatment success of abdominal pain AND stool consistency is absent for at least 3 weeks during a 4-week assessment period (an alternate possibility for the definition of recurrence will be the absence of treatment success of abdominal pain AND stool consistency for any 3 consecutive weeks).

Figure 3 Proposed Repeat Treatment Study Design



Abbreviations: RFX = rifaximin; PBO = placebo; f/u = follow-up; DBR = Double-Blind, Randomized; SRT = Second Repeat Treatment; and EOS = end of study.

*During the Maintenance Phases subjects with recurrence enter the Repeat Treatment Phases:
- Maintenance Phase 1: Subjects who do not meet recurrence criteria by the end of the 8 week Maintenance Phase will be allowed to continue up to an additional 12 weeks until they experience recurrence; or until enrollment is met in DBR (Repeat Treatment) Phase.
- Maintenance Phase 2: Subjects who do not meet recurrence criteria by the end of 8 weeks will be withdrawn from the study.

This study design consists of the following key phases:

- **Initial Rifaximin Treatment Phase (4 weeks):** All patients will receive rifaximin 550 mg TID for 2 weeks, with 2 weeks of treatment-free follow-up. This phase will select for responders, with non-responders discontinued from the trial.
- **Maintenance Phase 1 (up to 8 weeks):** Clinical responders will enter this treatment-free phase and will be assessed for persistence of response as well as recurrence of IBS symptoms. This phase will be variable in duration for patients, but will last a minimum of 2 weeks. Subjects who experience recurrence will be immediately transitioned into the Double-Blind, Randomized (Repeat Treatment) Phase.
- **Double-Blind, Randomized (Repeat Treatment) Phase (4 weeks):** Subjects with recurrence in Maintenance Phase 1 will be randomized 1:1 to receive rifaximin 550 mg TID or placebo TID for 2 weeks with a 2 week treatment-free follow-up. We propose that non-responders in the Double-Blind, Randomized (Repeat Treatment) Phase will be withdrawn from the study.
- **Maintenance Phase 2 (up to 8 weeks):** Responders in the Double-Blind, Randomized (Repeat Treatment) Phase will be eligible for Maintenance Phase 2 and will continue with an additional treatment-free follow-up period. Subjects who experience recurrence will be immediately transitioned into the Second Repeat Treatment Phase. We propose

that subjects still meeting criteria for response at the end of the 8-week Maintenance Phase be withdrawn from the study.

- **Second Repeat Treatment Phase (4 weeks) and End of Study: S**ubjects with recurrence in Maintenance Phase 2 will be eligible to enter the Second Repeat Treatment Phase. The treatment assignment from the first re-treatment will be maintained in this phase. At the end of this phase, subjects will undergo end of study assessments.

Salix has presented this study design based on extensive deliberations with key opinion leaders as well as discussions with the FDA. Salix believes the proposed design will provide the critical information needed to address points raised by the FDA in the CRL regarding the need for prospective and controlled data on rifaximin's efficacy following repeat treatment in IBS patients.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 2
1.1. IBS and Unmet Medical Need 2
1.2. Developing Therapies for IBS 2
1.3. Regulatory History of Rifaximin in IBS 3
1.4. Rifaximin Pharmacology 5
1.5. Clinical Efficacy 6
1.6. Clinical Safety 8
1.7. Rifaximin Repeat Treatment Study Proposal 9
2. REGULATORY BACKGROUND 19
2.1. Product Information 19
2.2. Currently Approved IBS Treatments in the United States 19
2.3. Rifaximin IBS Regulatory History in the United States 20
2.4. Patient Population in Rifaximin IBS Program 22
2.5. FDA Draft Guidance for IBS and Efficacy Endpoints 22
3. IRRITABLE BOWEL SYNDROME 24
3.1. IBS Background and Unmet Need 24
3.2. IBS Etiology and Development Challenges 24
3.3. Intestinal Dysbiosis and IBS 25
3.4. Diagnosis of IBS: Role of Biomarkers 26
3.5. Rifaximin for the Treatment of non-C IBS 27
4. RIFAXIMIN – MECHANISMS OF ACTION IN IBS 30
4.1. Mechanisms of Action 30
4.2. Microbiologic Resistance 32
4.3. Clinical Pharmacology 34
4.3.1. Pharmacokinetics 34
4.3.2. Pharmacodynamics 34
4.3.3. Absorption 34
4.3.3.1. Pharmacokinetics - IBS Subjects Versus Healthy Volunteers 35
4.3.3.2. Efflux Transport Studies 36
4.3.4. Distribution 36
4.3.5. Metabolism and Drug-Drug Interaction 36
4.3.5.1. In Vitro Studies 36
4.3.5.2. In Vivo Studies 37
4.3.6. Excretion 37
4.3.7. Dose Selection in TARGET 1 and TARGET 2 38
5. OVERVIEW OF THE COMPLETED CLINICAL DEVELOPMENT PROGRAM FOR IBS 39
5.1. TARGET 1 and TARGET 2 Study Design 39
5.1.1. Subject Population (TARGET 1 & TARGET 2) 40
5.1.2. Efficacy Endpoints (TARGET 1 & TARGET 2) 42

5.1.2.1. Primary Endpoint and Key Secondary Endpoint (TARGET 1 & TARGET 2) ..42
5.1.2.2. Secondary Endpoints - Daily Assessments of IBS Symptoms (TARGET 1 & TARGET 2) 42
5.1.2.3. FDA Abdominal Pain and Stool Consistency Endpoint (TARGET 1 & TARGET 2) 42
5.1.3. Subject Disposition in Phase 3 (TARGET 1 & TARGET 2) 43
5.1.4. Demographics and Baseline Characteristics in Phase 3 (TARGET 1 & TARGET 2) 43
5.2. RFIB2001 (Phase 2b) 45
5.2.1. Study Design (RFIB2001) 45
5.2.2. Subject Disposition, Demographics, and Baseline Characteristics (RFIB2001)...45
6. CLINICAL EFFICACY 46
6.1. Overview of Key Efficacy Results in TARGET 1 & TARGET 2 46
6.2. Primary Efficacy Endpoint – Adequate Relief of Global IBS Symptoms 49
6.2.1. Sensitivity Analyses of the Primary Endpoint 49
6.2.2. Subgroup Analyses of the Primary Endpoint....51
6.2.3. Efficacy Over Time - Adequate Relief of Global IBS Symptoms....52
6.2.3.1. Onset of Relief....52
6.2.3.2. Persistent Efficacy Analyses 52
6.2.3.3. Adequate Relief of Global IBS Symptoms During Weeks 7 through 12....53
6.3. Key Secondary Endpoint – IBS Bloating....54
6.4. Abdominal Pain and Stool Consistency – FDA Draft Guidance Endpoint 55
6.5. Rifaximin Impact on Individual IBS Symptoms Over 12 Weeks....56
6.6. Clinical Utility of Rifaximin 59
6.7. Phase 2b Study RFIB2001 60
6.7.1. Co-Primary Endpoints (RFIB2001)....60
6.7.2. Long Term Rifaximin Treatment Effect in RFIB2001 61
6.7.2.1. Other Efficacy Findings in RFIB2001 61
7. CLINICAL SAFETY 62
7.1. Summary of Supportive Safety Data....62
7.2. Evaluation of Safety Data in Patients with Non-C IBS 63
7.3. Overall Extent of Exposure....63
7.4. Subject Disposition....63
7.5. Summary of Adverse Events....64
7.5.1. Common AEs in TARGET 1, TARGET 2, and RFIB2001 64
7.5.1.1. Common Adverse Events in Phase 3 (TARGET 1 & TARGET 2) 65
7.5.2. AEs by Relationship and Intensity in TARGET 1 & TARGET 2, and RFIB2001....66
7.6. Deaths, SAEs, and AEs Leading to Discontinuation (TARGET 1 & 2, and RFIB2001) 66
7.6.1. Deaths 66
7.6.2. Serious Adverse Events 66

7.6.3. Adverse Events Resulting in Study Discontinuation 67
7.7. Adverse Events of Special Interest in IBS Population 67
7.7.1. Evaluation of Gastrointestinal Disorders 67
7.7.2. Evaluation of Infections 67
7.8. Clinical Laboratory Data 68
7.9. Adverse Events in Special Populations 68
7.10. Long-Term Safety Data 69
7.10.1. Summary of Long-Term Safety in Rifaximin HE Program 69
7.11. Evaluation of Bacterial Resistance 71
7.12. Supportive Safety Findings 72
7.13. Summary of Important Foreign Actions 72
8. PROPOSED RIFAXIMIN REPEAT TREATMENT STUDY 73
8.1. Repeat Treatment Study Design Considerations 73
8.2. Existing Data for Repeat Rifaximin Treatment in IBS 73
8.3. Proposed Repeat Treatment Study Design 75
8.3.1. Subject Population 77
8.3.2. Repeat Treatment Study Objectives and Endpoints 78
8.3.3. Analysis Populations and Efficacy Endpoints 80
9. REFERENCES 81

Appendix 1 XIFAXAN® Package Insert

LIST OF TABLES

Table 1 Overview of Safety Results from TARGET 1 and 2 (Combined Data Over 12 Weeks) 8
Table 2 Currently Available Drug Products for IBS in the US 20
Table 3 Rifaximin Drug Development Programs 20
Table 4 FDA-Recommended Endpoints for IBS with Diarrhea 23
Table 5 Mean (± SD) Plasma Pharmacokinetic Parameters of Rifaximin 550 mg TID in IBS Subjects (RFPK1010) and Healthy Volunteers (RFPK1007) 35
Table 6 Table of Completed Salix Clinical Studies 39
Table 7 Rome II: IBS Diagnosis and Subtyping 41
Table 8 Demographics and Baseline Characteristics for TARGET 1 & 2 (ITT Population) 44
Table 9 Subjects with Missing Data in the PEP – TARGET 1 & TARGET 2 50
Table 10 Adequate Relief of Global IBS Symptoms – Primary and Sensitivity Analyses Responders (TARGET 1 & TARGET 2) 50
Table 11 Analysis of Persistent Efficacy: Number of Months of Adequate Relief of Global IBS Symptoms – TARGET 1 & TARGET 2 53
Table 12 Analysis of Persistent Efficacy: Adequate Relief of Global IBS Symptoms Responders for All 3 Months – TARGET 1 & TARGET 2 53
Table 13 Average Treatment Effect from Weeks 7 through 12: Global IBS Symptoms – TARGET 1 & TARGET 2 54
Table 14 RFIB2001: Adequate Relief of Global IBS Symptoms and IBS-Related Bloating at the End of the Treatment Phase (Primary Comparison, ITT Population) 61
Table 15 Overall Summary of Adverse Event Incidence (TARGET 1, TARGET 2, and RFIB2001) 64
Table 16 Adverse Events in at Least 2% of Rifaximin- or Placebo-Treated Subjects (TARGET 1, TARGET 2, and RFIB2001) 65
Table 17 Adverse Events Occurring in at Least 2% of Rifaximin Subjects in Phase 3 (TARGET 1 & TARGET 2 Combined Data) 66
Table 18 Overview of Rifaximin Studies for Reduction in Risk of Overt HE Recurrence 69
Table 19 Existing Data for Repeat Rifaximin Use in IBS 74
Table 20 Rome III: IBS Diagnosis and Subtyping 78

LIST OF FIGURES

Figure 1 Highlights of Rifaximin IBS Development History 4
Figure 2 Impact of Rifaximin on Relief of IBS Symptoms During the PEP (Weeks 3-6) 7
Figure 3 Proposed Repeat Treatment Study Design 10
Figure 4 Chemical Structure of Rifaximin 19

Figure 5 Comparison of Rifaximin Plasma Exposure in IBS Subjects and Healthy Subjects with Plasma Exposure to Oral Antibiotics Used for IBS/SIBO Treatment 28
Figure 6 IBS Improvement Over 10 Weeks of Post-treatment Follow-up with Rifaximin Versus Placebo (Pimentel et al. 2006) 29
Figure 7 Study Design for TARGET 1 and TARGET 2 40
Figure 8 Subject Disposition for TARGET 1 & TARGET 2 43
Figure 9 Relief of IBS Symptoms during the PEP (Weeks 3-6) – TARGET 1 & TARGET 2...46
Figure 10 Global IBS Symptoms Responders at Each Month, Based on Weekly and Daily Measures in TARGET 1 and TARGET 2 (Point Prevalence Analysis) 47
Figure 11 Impact of Rifaximin on Relief of IBS Symptoms Over 3 Months in the TARGET Studies – Number of Months Analysis 48
Figure 12 Efficacy Endpoint Responders for the Entire 3 Months of the TARGET Studies.....48
Figure 13 Adequate Relief of Global IBS Symptoms (TARGET 1 & 2 and Combined Data).....49
Figure 14 Subgroup Analyses: Adequate Relief of Global IBS Symptoms Responders (ITT Population – TARGET 1 & 2 Combined Data) 51
Figure 15 Cumulative Response Curve for Adequate Relief of Global IBS Symptoms (Primary Endpoint – TARGET 1 & TARGET 2 Combined Data).....52
Figure 16 Adequate Relief of IBS Bloating (TARGET 1 & 2, and Combined Data).....55
Figure 17 Abdominal Pain and Stool Consistency Endpoint Responders (TARGET 1 & 2, and Combined Data) 56
Figure 18 GLOBAL IBS SYMPTOMS: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 - ITT Population) 57
Figure 19 IBS BLOATING: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 - ITT Population).....57
Figure 20 ABDOMINAL PAIN AND DISCOMFORT: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 - ITT Population).....58
Figure 21 STOOL CONSISTENCY: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 - ITT Population).....58
Figure 22 STOOL URGENCY: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 -ITT Population).....59
Figure 23 Rifaximin, Alosetron, Tegaserod, and Lubiprostone Number-Needed-to-Treat 60
Figure 24 Safety Population of Subjects in Rifaximin Clinical Studies 62
Figure 25 Survival Analysis for Subjects Who Died Within 30 Days of Last Dose (RFHE3001).....70
Figure 26 Duration of Benefit Between Re-Treatments with Rifaximin 75
Figure 27 Proposed Repeat Treatment Study Design.....76

List of Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACG	American College of Gastroenterology
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{tau}	AUC from time 0 to end of the dosing interval, tau
AUC_{0-t}	AUC from time 0 (predose) to the last quantifiable concentration-time point
$AUC_{0-\infty}$	AUC from time 0 (predose) to infinity
BID	twice daily
BSEP	bile salt export pump
C. difficile	*Clostridium difficile*
CI	confidence interval
CL/F	oral clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CRL	Complete Response Letter
CYP	cytochrome
DBR	Double-blind, Randomized
EAEC	enteroaggregative *Escherichia coli*
E. coli	*Escherichia coli*
EE	ethinyl estradiol
EOP2	end of phase 2
EOS	end of study
ETEC	enterotoxigenic *E. coli*
FDA	Food and Drug Administration
GI	gastrointestinal
GIDAC	Gastrointestinal Drugs Advisory Committee
GBT	glucose hydrogen breath tests
HE	hepatic encephalopathy
IBS	irritable bowel syndrome
IBS-C	constipation-predominant IBS
IBS-D	diarrhea-predominant IBS
IC_{50}	50% inhibitory concentration
IND	Investigational New Drug Application
ISS	Integrated Summary of Safety
ITT	intent-to-treat
IVRS	interactive voice response system
LBT	lactulose hydrogen breath test

LOCF	last observation carried forward
MIC	minimal inhibitory concentration
MIC_{50}	MIC that inhibits 50% of microorganism growth
MIC_{90}	MIC that inhibits 90% of microorganism growth
NDA	New Drug Application
NG	norgestrel
NGMN	17-deacetylnorgestimate
NNT	number needed to treat
non-C IBS	non-constipation IBS
OC	oral contraceptive
PBO	placebo
PEP	primary evaluation period
PEY	person exposure years
P-gp	P-glycoprotein
PP	per protocol
PRO	patient-reported outcome
PXR	pregnane X receptor
QTc	heart-rate–corrected QT
Rc	accumulation ratio
RFX	rifaximin
RPOB	RNA polymerase beta-subunit encoding gene
SAE	serious adverse event
Salix	Salix Pharmaceuticals Inc.
SD	standard deviation
SGA	subject global assessment
SIBO	small-intestinal bacterial overgrowth
sNDA	supplemental NDA
SRT	Second Repeat Treatment
TARGET 1	Study RFIB3007
TARGET 2	Study RFIB3008
TD	travelers' diarrhea
TID	3 times daily
$t_{½}$	terminal or disposition half-life
T_{max}	time to C_{max}
TRX	treatment
ULN	upper limit of normal
US	United States

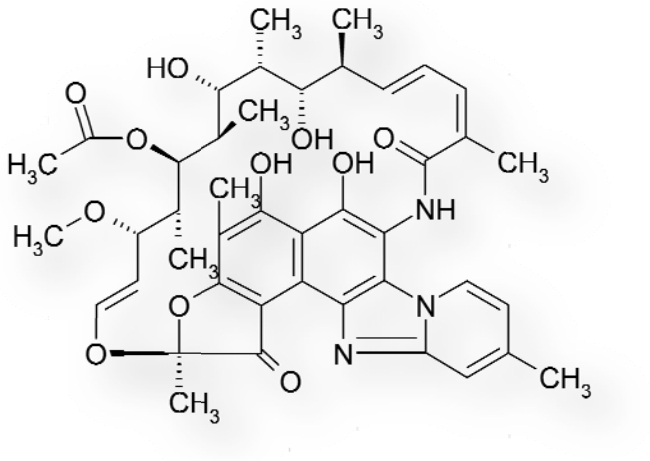
2. Regulatory Background

2.1. Product Information

Rifaximin is a semi-synthetic, nonsystemic antibiotic. Rifaximin is currently approved in the US for the treatment of TD caused by noninvasive strains of *E. coli* in patients ≥ 12 years of age (400 mg TID for 3 days), and for the reduction in risk of overt HE recurrence in patients ≥ 18 years of age or older (550 mg BID as chronic, daily therapy).

The chemical structure of rifaximin is presented in Figure 4. The chemical name is (2S,16Z,18E,20S,21S,22R, 23R,24R,25S,26S,27S,28E)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino) benzofuro[4,5-e]pyrido[1,2-á]-benzimidazole-1,15(2H)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$ and its molecular weight is 785.9.

Figure 4 Chemical Structure of Rifaximin



2.2. Currently Approved IBS Treatments in the United States

There is an unmet medical need in the US for effective and safe therapies for the treatment of IBS (Table 2). Despite the debilitating and life-altering symptoms associated with IBS, treatment options for patients are limited, particularly for IBS associated with diarrhea. Treatments aimed at relieving individual IBS symptoms (e.g., antispasmodics, anti-diarrheal agents, bulking agents, anti- flatulence agents) fail to address the entire syndrome complex and have not proven to be more effective than placebo in improving global IBS symptoms and reducing pain and bloating.[86,87]

Previously approved drugs have demonstrated efficacy by altering GI motility and gut hypersensitivity. While somewhat effective at "normalizing" motility, these approaches require daily therapy to maintain an effect and have been associated with safety concerns.[13,14,15,16,25] Two serotonin modulating agents approved by the FDA, Lotronex® (alosetron) for IBS-D and Zelnorm® (tegesarod) for IBS-C, have been associated with serious side effects leading to market withdrawals.

After being withdrawn from the market in November 2000 due to safety concerns, Lotronex was re-introduced in 2002 under a restricted access program.

Table 2 Currently Available Drug Products for IBS in the US

Drug product	Hypothesized mechanisms of action	Indication	Efficacy and Safety Highlights
Lotronex® (Alosetron)	5-HT_3-antagonists	IBS-D	• Approved only for females with severe, chronic IBS-D who fail conventional therapy; physicians must complete a prescribing program and patients must sign a patient acknowledgement form. • Boxed Warning for serious GI adverse reactions: ischemic colitis and life-threatening complications of constipation.
Amitiza®[88] (Lubiprostone)	Chloride-channel activator	IBS-C and CIC	• Approved for IBS-C in women. • Noted side effects: diarrhea, nausea, and abdominal pain.

Abbreviations: US = United States; CIC=chronic idiopathic constipation; IBS=irritable bowel syndrome; IBS-D=diarrhea-predominant IBS; and IBS-C=constipation-predominant IBS.

2.3. Rifaximin IBS Regulatory History in the United States

Salix has worked closely with the FDA on the IBS development program for rifaximin, and in the development programs for other indications, including approvals for rifaximin in the treatment of TD and prevention of recurrence of overt HE. Table 3 summarizes the major development activities in the US. Current XIFAXAN® labeling is provided in Appendix 1.

Table 3 Rifaximin Drug Development Programs

Indication	Regulatory Status	Dosage
Irritable bowel syndrome	Phase 3 complete NDA Submitted June 2010 Complete Response issued March 2011	550 mg tablets 3 times daily for 14 days
Hepatic encephalopathy	Approved March, 2010	XIFAXAN® 550 mg tablets twice daily, as chronic, daily therapy
Travelers' diarrhea	Approved May, 2004	XIFAXAN® 200 mg tablets 3 times daily for 3 days

In October 2005, Salix met with the FDA Division of Gastroenterology Products to discuss the use of rifaximin in the treatment of IBS. Based on recommendations from the FDA, Salix designed and performed the phase 2b, dose-ranging study RFIB2001. In accordance with the recommendations from the FDA the study included a 3 month post-treatment follow-up to ascertain durability of response.

Following completion of RFIB2001, an End-of-Phase 2 (EOP2) meeting was held with the FDA to gain agreement on key development issues regarding the phase 3 program and filing an NDA. The following key issues were discussed at the EOP2 meeting:

- Salix proposed a 6-week phase 3 study to evaluate the safety and efficacy of rifaximin 550 mg TID based on findings from RFIB2001. The FDA recommended 2 phase 3 trials of 12 weeks in duration, as IBS is a chronic syndrome. In accordance with these recommendations, the phase 3 studies were designed for 12 weeks, including a 2 week treatment phase and a 10 week post-treatment follow-up phase. The primary evaluation

period (PEP), defined as Weeks 3-6, was deemed acceptable by the FDA to demonstrate short-term efficacy for rifaximin in IBS. All efficacy endpoints were assessed every 4 weeks (i.e., Weeks 4, 8, and 12 or Months 1, 2, and 3) over the 12 week duration.

- TARGET 1 and TARGET 2 were designed to confirm efficacy following a short course of therapy. The trials were powered to evaluate response at Weeks 3 through 6 following a 2-week course of rifaximin vs. placebo.
- The FDA raised the issue of possible recall bias in the proposed weekly adequate relief endpoints. In accordance with their recommendations, Salix collected and analyzed daily assessments of IBS symptoms in phase 3 in addition to the weekly assessments.

A pre-NDA meeting was held in December 2009, following the completion of phase 3 (TARGET 1 & 2), to evaluate the status of the development program and the content and format of the proposed sNDA. The following key issues were discussed at the pre-NDA meeting:

- The FDA acknowledged prior agreements with Salix on the primary endpoint and that the endpoints pre-specified in the protocol would be used to support approval. The FDA noted the data for the treatment effect in the endpoints should be supported by both the individual trial data and the pooled data between studies.
- The FDA presented their new approach to IBS trial design and analysis for IBS products. At the Agency's request, Salix agreed to additional analyses of the phase 3 IBS data using a composite endpoint of abdominal pain and stool consistency responders. These analyses would be considered exploratory; however, "statistical and clinical significance of the new endpoints would be reviewed favorably." Subsequently, the FDA published draft guidance on the clinical evaluation of drugs in IBS (March 2010) with the composite endpoint.
- The FDA agreed that the safety of rifaximin during long-term exposure could be established using data from the rifaximin HE program.

Following the pre-NDA meeting Salix submitted a sNDA for rifaximin for the non-C IBS indication in June 2010 with the following proposed indication statement: "The treatment of non-C IBS and IBS-related bloating in patients ≥ 18 years of age." The recommended dose of rifaximin for non-C IBS was 550 mg taken orally TID for 14 days.

During the review of the NDA, Salix and the FDA had extensive discussions about how best to handle the durability analyses. Salix's position is that medicines with short course therapy (e.g., rifaximin in IBS, certain treatments for acute pain), should establish "immediate" benefit followed by persistent relief. In line with the Agency recommendation to access efficacy at Weeks 4, 8 and 12, Salix provided data to the FDA following the understanding that analyses to determine "durability" for a short course of therapy needed to demonstrate both rapid and persistent effect.

On March 7, 2011 the FDA issued a CRL for the rifaximin IBS application. In the CRL, the FDA requested evidence that rifaximin is effective in the repeat treatment of IBS following recrudescence of symptoms. After receipt of the CRL, Salix met with the FDA on several occasions to discuss appropriate paths forward toward approval. To that end, Salix has worked collaboratively with the FDA over the last several months to discuss necessary study design elements for a repeat treatment protocol. Based on these meetings with the FDA, Salix has

developed a study proposal intended to assess the benefit of repeat rifaximin treatment in IBS patients.

A meeting of the GIDAC was scheduled for November 16, 2011 to discuss the rifaximin sNDA and to evaluate the adequacy of the repeated treatment study proposal.

2.4. Patient Population in Rifaximin IBS Program

Rifaximin 550 mg is proposed for the treatment of non-C IBS and IBS-related bloating in patients ≥ 18 years of age. Subjects in the rifaximin IBS program were currently experiencing diarrhea and were not experiencing symptoms of constipation during the ≥7 day eligibility period prior to the first dose of study drug. Thus, the studies support an indication of IBS without constipation.

In phase 2 and phase 3, subjects were diagnosed with IBS using the Rome II criteria (see Table 7 in Section 5.1.1). The Rome criteria are the clinical standard for diagnosing and subtyping IBS. The Rome criteria were used to define IBS populations for previously approved drugs, and are consistent with FDA guidance.[89,90,91] In phase 3, the Rome criteria were coupled with specific requirements for watery or loose stools and IBS related bloating (included in the original Manning Criteria for diagnosing IBS), and subjects with confounding medical conditions and/or medications were excluded. These entry criteria provided rigorous characterization of a population likely to have IBS related to enteric bacterial dysbiosis (see Sections 3.3 and 3.5).

The enrolled population in phases 2 and 3 were predominately considered to be IBS-D patients based on the Rome II criteria at the time of study entry. At present, the FDA's draft guidance does not address the clinical evaluation of subjects with mixed or alternating IBS. While these patients are estimated to comprise one-third of the IBS population, they can be difficult to define and evaluate for clinical trials. Salix believes that rifaximin offers clinical benefit to both IBS-D patients and to alternating or mixed IBS patients in a protracted diarrhea state. In contrast with previously approved agents such as alosetron, rifaximin's potential mechanisms of action in IBS would not be expected to have any lasting effects on gut motility that would likely pose a risk to any individual patient re-entering a constipation state. Therefore, in alternating or mixed IBS patients, it is not likely that rifaximin would promote a rebound effect to a constipation state or exacerbate constipation should it emerge during treatment.

2.5. FDA Draft Guidance for IBS and Efficacy Endpoints

In March 2010 the FDA released draft guidance for industry, "Irritable Bowel Syndrome – Clinical Evaluation of Products for Treatment." The guidance addressed 3 main topics regarding IBS symptom assessments: the evolution of IBS clinical trials; interim recommendations for IBS clinical trial design and endpoints; and future development of patient-reported outcome (PRO) instruments for use in IBS clinical trials. The guidance notes that measuring treatment benefit in IBS clinical trials can be challenging, as a reliable biological marker for IBS has not been identified. For future IBS development, the guidance advocates the creation of new, content-valid PRO instruments that capture all of the clinically important signs and symptoms of IBS.

In the absence of these instruments, the FDA acknowledges the present unmet need to develop effective therapies for patients with IBS, and provides interim strategies and endpoints for IBS drug development. For IBS with diarrhea, the FDA guidance proposes the use of co-primary endpoints that include 2 of the major symptoms: abdominal pain and stool consistency (Table 4).

These endpoints are designed to be more symptom-specific than global IBS construct endpoints and to address the common definition of IBS from Rome III as abdominal pain or discomfort that is improved by defecation.

Table 4 FDA-Recommended Endpoints for IBS with Diarrhea

Co-Primary endpoint	Entry criteria	Responder Definition
Pain Intensity AND **Stool Consistency**	**Pain Intensity** Weekly average of worst abdominal pain in past 24 hours score of ≥ 3.0 in a 0 to 10 point score	**Pain Intensity** Decrease in weekly average of worst abdominal pain in past 24 hours score of ≥ 30% compared with baseline
	Stool Consistency Weekly average ≥ Type 6 by the Bristol stool score.	**Stool Consistency** Weekly average ≤ Type 5 by the Bristol stool score.
		'Classification as a responder involves achieving a prespecified improvement in symptoms at least 50 percent of the time.'

Source: Guidance for Industry. Irritable bowel syndrome: Clinical evaluation of products for treatment. FDA Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER); March 2010.

In light of the ongoing debate regarding the utility of various endpoints in IBS trials, rifaximin was evaluated using multiple endpoints in the IBS development program. These included subject global assessment (SGA) adequate relief endpoints, consistent with primary endpoints utilized during 20+ years of IBS trial design; daily assessment endpoints designed to eliminate concerns of patient recall bias; and abdominal pain and stool consistency endpoints consistent with the FDA draft guidance for the clinical evaluation of products for IBS (Table 4). A consistent and significant rifaximin treatment effect in IBS patients was observed in each of these endpoints across the TARGET studies (Section 6). This consistency demonstrates the robustness of rifaximin's efficacy in providing relief of IBS symptoms in the non-C IBS population.

The primary endpoint was the proportion of subjects who achieved adequate relief of global IBS symptoms, assessed using a weekly SGA question. Similar binary endpoints addressing the construct of relief (e.g., adequate relief or satisfactory relief) have been a standard for primary outcome assessment in IBS trial design dating back more than 20 years.[92,93,94,95,96,97] These endpoints allow patients to integrate their symptoms and normalize assessment of efficacy to the patient's perspective of improvement. Responses are clinically relevant because they reflect the patient's assessment of relief or no relief from IBS symptoms. Based on multiple data analyses and reviews, thought leaders in IBS and the Rome Foundation advocate for the continued use of a binary endpoint, such as adequate relief, as a valid endpoint for IBS clinical trials.[92,93,94,95,96,97,98]

For the proposed repeat treatment study, Salix will utilize the primary endpoint from the FDA's draft guidance (see Section 8.3.3). The repeat treatment study will also include endpoints for weekly assessments of global IBS symptoms and IBS bloating, and daily assessment endpoints for key IBS symptoms.

3. Irritable Bowel Syndrome

3.1. IBS Background and Unmet Need

Irritable bowel syndrome is a heterogeneous GI disorder characterized by chronic recurring, remitting symptoms, including abdominal pain, bloating, and abnormal defecation (constipation, diarrhea, or both) in the absence of structural or biochemical abnormalities.[1,2,3,4,5,7,8,9] Although most people experience GI disturbances at some time during their lives, IBS patients have more frequent and severe symptoms, and are more likely to have symptoms that lead to distress and disrupt their work, lifestyle, and well-being. The symptoms of IBS cause substantial impairment in health-related quality of life and lead to increased health resource utilization and reduced work productivity.[1,3,4,5,8,9] As noted by the American College of Gastroenterology (ACG) task force on IBS, patients with IBS "visit the doctor more frequently, use more diagnostic tests, consume more medications, miss more workdays, have lower work productivity, are hospitalized more frequently, and consume more overall direct costs than patients without IBS."[7] Studies have shown that people with IBS can have a lower quality of life than those with heart disease and other chronic medical conditions.[99]

There is no recognized physical abnormality or biological marker to define IBS. Therefore diagnosis is based on the presence of several characteristic symptoms (initially described using the Manning criteria) and the exclusion of other structural, metabolic, and physiologic disorders that would otherwise explain the symptoms of IBS. The criteria for diagnosis has been refined in the last 20 years by the Rome Foundation, beginning with the Rome I criteria (1992) and, more recently, the Rome II and Rome III criteria.[100,101] Modern convention further categorizes patients with IBS into diagnostic subtypes based on the predominance of either diarrhea or constipation (i.e., IBS-D, IBS-C), or the state of alternating between periods of diarrhea and constipation (i.e., mixed IBS or alternating IBS).

In the US, there is a great health and economic impact due to IBS. The prevalence of all forms of IBS appears to be 10% to 15% of the general population, and IBS is one of the leading reasons for consultation with a primary care physician.[1,7] Irritable bowel syndrome accounts for 3.5 million doctor visits annually in the US, and is associated with estimated annual direct costs of $10 billion and annual indirect costs of $20 billion.[10] Although IBS has a high prevalence, research has shown that a majority (>75%) of people with IBS are not medically diagnosed. For example, in a community survey published in 2005, the prevalence of IBS in 5009 subject screening interviews was 14.1%, however only 3.3% of respondents had been medically diagnosed.[102]

Despite the debilitating symptoms of IBS, treatment options for patients remain limited. Reasons for this include, but are not limited to, the heterogeneous nature of IBS, subjective and variable nature of the symptoms and lack of an objective response tool to measure relief. Historically, pharmaceutical companies have focused research and development efforts aimed at altering gastrointestinal motility and gut hypersensitivity. While somewhat effective at "normalizing" motility and alleviating certain symptoms, these approaches require chronic, daily therapy and some have safety concerns and/or a high potential for drug-drug interactions.[13,14,15,16,25]

3.2. IBS Etiology and Development Challenges

The exact cause of IBS remains unknown. IBS has traditionally been characterized as a disorder involving an altered brain-gut axis that can be associated with GI hypersensitivity and GI motor

dysfunction.[17,18] In the 1990s, studies demonstrated that abnormal gut motility was commonly found in patients diagnosed with IBS. The most prominent molecule in the mediation of neuromuscular control of transit is serotonin and this transmitter was a major focus for drug development (see Section 2.2). Serotonin-modulating agents showed efficacy in treating IBS symptoms when those agents were dosed on a chronic basis, but were also associated with serious safety concerns.

More recent research has focused on new theories that have identified specific etiological or precipitating factors for IBS symptoms. These factors include alterations in the normal intestinal microbiota, pathogenic bacterial infection, genetic pre-determinants, altered gut immune function, and inflammation.

3.3. Intestinal Dysbiosis and IBS

In recent years, the human microbiome, its diversity and its equilibrium have become increasingly recognized as having significant influence on human health. Multiple microbiome populations are under study, including those of the skin, mucosal surfaces, and GI tract, with the largest population in the colon. This influence has been described quantitatively; the microorganisms living inside or on a human outnumber the cells of their host by a factor of approximately 10.[103]

While the exact role of the GI microbiota, whether it be of the small intestine, large intestine or both, in the pathophysiology of IBS is not completely understood, bacterial dysbiosis may be best viewed as a quantitative or qualitative imbalance which results in the symptoms of IBS, and not an infection *per se*. Epidemiologic, physiologic, and clinical evidence has emerged suggesting that dysbiosis of the GI microbiota is important in the pathogenesis of IBS and may be a target for therapy.[38,39,40,41,42] The GI microbiota in IBS patients have been shown to have less diversity and stability than in healthy subjects.[33,40,41,42] As the GI microbiota play a major physiological and immunological role, this disequilibrium is believed to be an important factor in the emergence of IBS symptoms in certain patients.

Several lines of evidence demonstrate a key role for bacterial dysbiosis in the etiology of IBS. Epidemiological studies have strongly linked the development of IBS to previous experience with infectious GI events, such as TD or gastroenteritis; infectious diarrhea caused by *Salmonella*, *Shigella*, or campylobacter precedes IBS onset in up to 30% of patients that experience an acute event of infectious diarrhea.[28,29,30,31,104,105] In these cases, the initial pathogen may result in lingering dysbiosis and a resulting low-grade inflammatory response. Additionally, IBS symptoms have been correlated to the presence of bacteria in the small intestine in quantities greater than those observed in healthy controls.[106,107,108,109] Eradication or modulation of this bacterial overgrowth has also been shown to correlate with improvement in IBS symptoms.[2,38,110,111]

Specific to the microbiome of the small intestine, there is evidence pointing to a role for SIBO in IBS.[38,40,41,42,112] Increases in bacterial counts in the small intestine can lead to increased fermentation, gas production, and altered gut motility. The presence of SIBO has been shown to be prevalent in a large number of IBS patients and the symptoms of IBS are similar to the symptoms of SIBO, including bloating, abdominal discomfort, and diarrhea.[38,40,41,42]

Other evidence suggests that IBS may be linked to subtle qualitative changes in the gut microbiota.[33] These changes may include the proliferation of species that produce more gas and

short chain fatty acids, and are more active in the deconjugation of bile acids.[33,34,35] The deconjugation of bile acids could profoundly affect colonic motility by changing water and electrolyte transport in the gut.

The interaction between altered gut flora and the gut mucosa in IBS patients may also be of importance. Evidence suggests that altered gut microbiota may lead to immune activation and inflammation in the colonic mucosa, which may promote or exacerbate the symptoms of IBS.[36,37] Up to one third of the patients that recover from intestinal bacterial infection (e.g., gastroenteritis) display subsequent symptoms consistent with IBS.[113,114] This represents a link between bacteria and inflammation in the etiology of IBS.

3.4. Diagnosis of IBS: Role of Biomarkers

At present, there is no definitive diagnostic tool or reliable biological marker for IBS, which is the basis for patient-reported symptom assessments such as the Rome criteria as the clinical standard for diagnosing and subtyping IBS.

Attempts to diagnose IBS with a variety of biomarkers have been disappointing, with no single biomarker proving to be sensitive or specific.[115,116,117] A panel of 10 biomarkers has been proposed for the diagnosis of IBS-D.[117] This panel appears to be mostly based on the exclusion of other potential causes of diarrhea and abdominal pain and/or bloating such as celiac disease and inflammatory bowel disease. The predictive value of this biomarker panel did not appear to exceed that determined by the Manning or Rome criteria.[118]

The emerging evidence of a link between IBS and GI microbiota has sparked interest in identifying potential antibiotic-responsive IBS patients by identifying the presence of SIBO. This interest in SIBO is due to the close overlap in symptoms between IBS and SIBO, as well as reports of an increased prevalence of SIBO among IBS patients.[119,120] There is no validated diagnostic tool for SIBO however, making identification of IBS patients with SIBO difficult and clinically impractical due to limitations of available techniques:

- **Aspiration and direct culture of jejunal contents:** Jejunal aspirates are the reputed gold standard for identifying SIBO, but small intestinal culture methods are invasive and can present greater risks for IBS patients than potential benefits. Jejunal aspirates are associated with controversies surrounding the lack of standardization of location in the small bowel for sampling and how best to avoid proximal gut bacteria from causing contamination.[43] The current instrumentation utilized are limited in their ability to reach far enough into the small bowel to adequately diagnose bacterial overgrowth and culturing sites other than those in which the overgrowth is present can result in false negative diagnoses. There is no consensus estimate on the definition of a positive culture. SIBO is usually defined as a total growth of $\geq 10^5$ cfu/mL of intestinal fluid, however, this definition includes Gram-positive flora, which in turn includes upper respiratory flora, which has not been correlated with SIBO symptoms.[44]
- **Breath testing:** Indirect breath testing, such as lactulose hydrogen breath tests (LBT) and GBT, emerged as less invasive detection methods to detect SIBO when compared to jejunal aspirates.[43] However, breath testing continues to be controversial and challenging and provides inconsistent results. Currently, ACG does not recommend breath testing to identify SIBO in IBS patients.[121]

Both LBT and GBT are associated with limitations in their reliability in diagnosing SIBO. Lactulose breath tests have low sensitivity and specificity, and consequently have the potential for false positive diagnoses. Glucose breath tests by contrast are less sensitive but more specific, but can underestimate overgrowth allowing for false negative results.[44,45]

Breath testing has also come into question recently with studies suggesting that test results with the LBT are influenced both by the orocecal transit time as well as the criteria used to define a positive test.[119,122] In such circumstances the role of bacteria in the small bowel cannot be excluded or confirmed as rapid transit through the small intestine may mask an otherwise early rise in breath hydrogen.[45,123] A combination of orocecal scintigraphy and breath testing may aid with interpretation but would not be practical on a routine basis.[119]

3.5. Rifaximin for the Treatment of non-C IBS

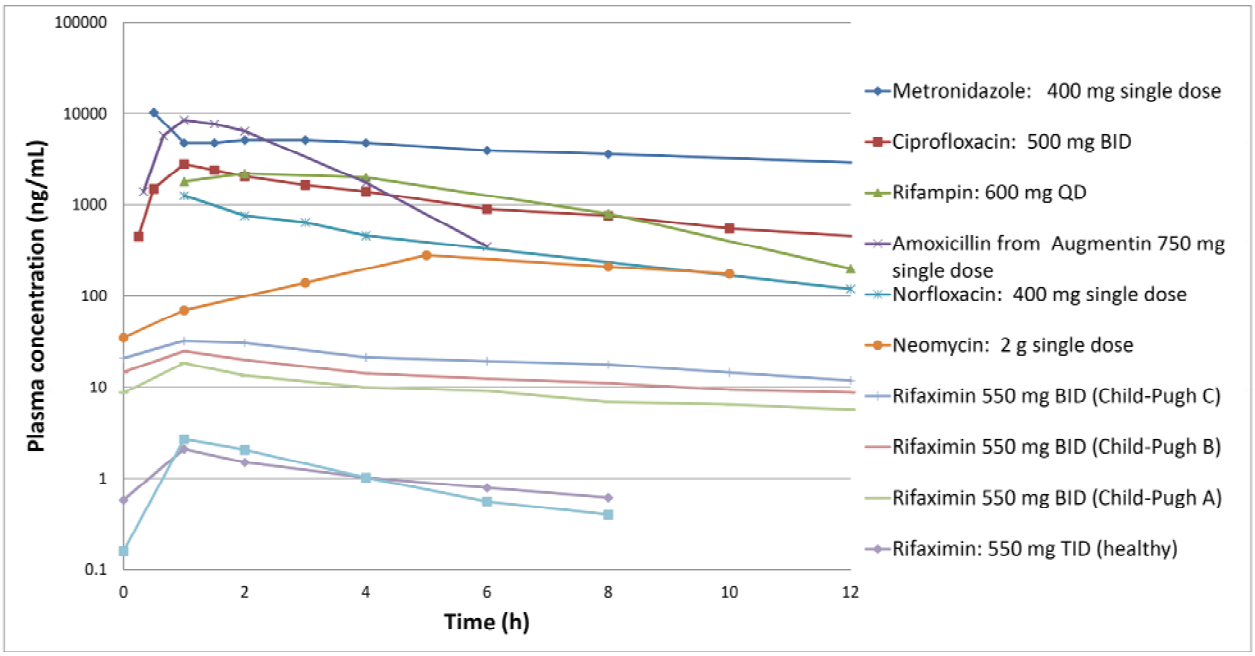
The evidence for a bacterial etiology in IBS raised the possibility of a new treatment paradigm. Early clinical experience with several antibiotics (i.e., metronidazole, neomycin, ciprofloxacin, and doxycycline) indicated that antibiotic therapy had a potential treatment benefit for IBS.[38,110]

While antibiotic therapy showed promise, investigation of several systemic and/or broad-spectrum antibiotics revealed suboptimal efficacy, and the potential for significant plasma exposure with an accompanying significant risk of adverse effects (e.g., nephrotoxicity and ototoxicity with aminoglycosides, tendon rupture with fluoroquinolones) and drug interactions.[124,125,126] Further, broad-spectrum antibiotics frequently eradicate beneficial gut flora, thereby putting the patient at risk for altered gut symbiosis and potential overgrowth by pathologic bacteria, including *C.difficile*.[127] Rifaximin is the first antibiotic to demonstrate robust, immediate and persistent symptom relief following a short course of therapy without concerns of systemic exposure in patients with IBS.

While the precise mechanism by which rifaximin exerts a beneficial effect on the symptoms of IBS are not fully known, there are a number of pharmacological and clinical pharmacological findings that could plausibly be linked to rifaximin's effect. Rifaximin has demonstrated a beneficial treatment effect in a variety of conditions in which host intestinal dysbiosis or disequilibrium plays a role in symptoms, including TD, HE, Crohn's disease, ulcerative colitis, diverticulitis, and IBS. Rifaximin has multiple in vivo and in vitro attributes that could explain its role in IBS associated with bacterial dysbiosis and differentiate it from systemic broad-spectrum antibiotics.[128,129,]

Rifaximin is a well characterized drug with no currently known drug interactions, and has negligible systemic absorption in comparison to other available antibiotic choices. Systemic broad-spectrum antibiotics have significant plasma exposure and an accompanying risk of adverse effects, including attenuation of beneficial gut flora, and frequent likelihood of drug interactions. Rifaximin by contrast has minimal systemic exposure (with plasma concentrations several orders of magnitude below those of systemic antibiotics; see Figure 5), high concentrations in the GI lumen, no significant eradication of normal stool flora, and no clinically significant drug interactions. Aside from rifaximin's in vitro antimicrobial activity, rifaximin also has effects related to host response as well as sub-MIC effects on bacterial metabolism, and virulence and adhesion. Additionally, in vivo, rifaximin does not appear to cause the drastic alterations in beneficial GI microbiota or clinically important bacterial resistance associated with potent broad-spectrum antibiotics.[71,72,73]

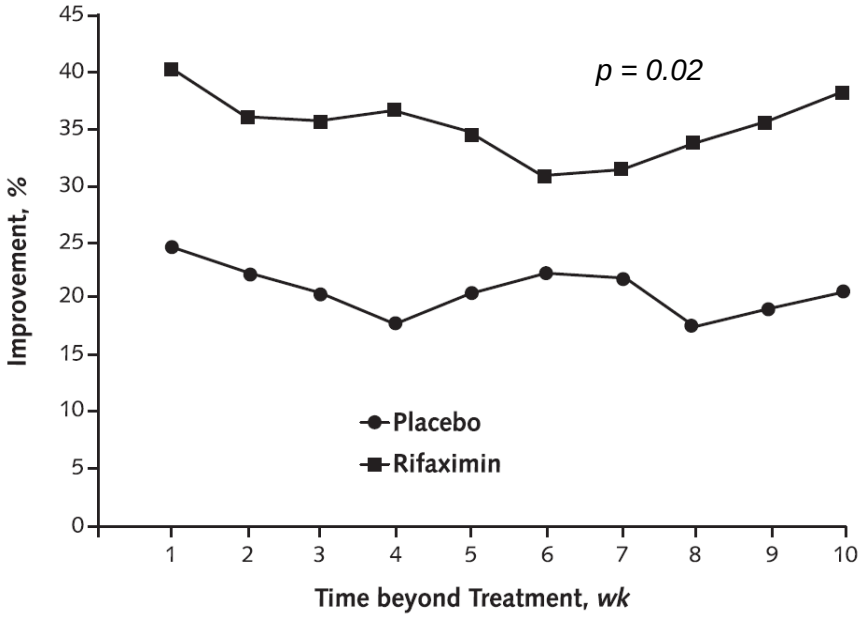
Figure 5 Comparison of Rifaximin Plasma Exposure in IBS Subjects and Healthy Subjects with Plasma Exposure to Oral Antibiotics Used for IBS/SIBO Treatment



The potential utility of rifaximin in the treatment of IBS associated with SIBO was recognized based on rifaximin's positive effect in the treatment of bloating, abdominal pain and diarrhea in SIBO-diagnosed patients. Rifaximin was effective in SIBO in several studies from the literature.[130,131,132,133,134,135] In some of these studies, reduction in SIBO correlated with improvement in symptoms also indicative of IBS. As noted in Section 3.3, a large number of IBS patients are believed to have SIBO. Given the similarities in the presentation of IBS and SIBO, and the emergence of other important shifts in the GI microbiota of IBS patients researchers began to explore rifaximin treatment in IBS.

Rifaximin's efficacy in the treatment of IBS was first demonstrated by results from double-blind, placebo-controlled studies in IBS patients in the published literature.[39,77] In a study conducted by Pimentel and colleagues in 87 subjects (44 placebo, 43 rifaximin), with IBS confirmed using Rome I criteria, treatment with rifaximin for 10 days (400 mg TID) resulted in significantly greater ($p = 0.02$) improvement in IBS symptoms over 10 weeks of treatment follow-up compared with placebo (Figure 6). Treatment with rifaximin also resulted in a significant improvement ($p = 0.01$) in bloating score over the 10-week treatment follow-up.[39]

Figure 6 IBS Improvement Over 10 Weeks of Post-treatment Follow-up with Rifaximin Versus Placebo (Pimentel et al. 2006)



Source: Pimentel et al. 2006
Mean improvements after 10 weeks: 36% rifaximin vs. 21% placebo (p = 0.020). The p-value represents the treatment group effect for the 10-week period on the outcome of the percentage of global improvement. The group-by-week interaction and week effects were not statistically significant; therefore, rifaximin was the main factor associated with the improvement.

Similar positive effects for rifaximin on the symptoms of abdominal bloating and flatulence were reported in another study of 124 subjects with chronic abdominal bloating and flatulence, 70 of whom also had IBS as determined by Rome II criteria.[77] After 10 days of treatment with rifaximin (400 mg TID), there was a significant difference in global symptom relief versus placebo (41% vs. 23%, p = 0.03). Among the IBS patients, a favorable response with rifaximin was also noted after 10 days of treatment (41% vs. 18%; p = 0.04) which persisted over another 10 days of follow up observations (27% vs. 9%; p = 0.05).

In 2 retrospective chart reviews of IBS patients, rifaximin treatment resulted in significant improvement in the symptoms of IBS versus neomycin ($p < 0.01$), and significant improvement in IBS symptoms at progressively higher daily doses (800, 1200, or 1800 mg/day).[84,136]

Several of these studies were included in a review of rifaximin in the treatment of IBS. The authors of this review concluded that rifaximin therapy for approximately 10 days in divided doses resulted in significant improvement in IBS symptoms.[137]

While rifaximin treatment demonstrated consistent benefit in studies in the literature, larger studies were necessary to confirm and fully characterize the benefit of rifaximin in IBS subjects. Salix initiated the development program for rifaximin in IBS beginning in 2005. These studies are discussed in Section 6 of this Briefing Document.

4. Rifaximin – Mechanisms of Action in IBS

4.1. Mechanisms of Action

While the precise mechanism by which rifaximin exhibits its therapeutic clinical effects is not known, several mechanisms may contribute to the beneficial effects of the drug in chronic GI disorders, including IBS.

Rifaximin is poorly absorbed and the drug's site of action is localized in the GI tract. This gut-targeted localization allows for treatment of enteric bacteria without systemic effects. In vitro and in vivo data document that rifaximin has multiple mechanisms that may contribute to its efficacy in IBS that are not ascribed to other antibiotics. Mechanisms that are separate from direct bactericidal activity and that may contribute to the efficacy of rifaximin include alterations in bacterial response and signaling, host-bacteria interactions, and host responses.

Antimicrobial Effects

Rifaximin inhibits bacterial protein synthesis by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase;[47] this binding activity results in suppression of RNA chain initiation during RNA synthesis. *Clostridium* species were found to be some of the most sensitive organisms to rifaximin with MIC_{90} = 0.005 - 2 µg/mL; rifaximin activity against *C. difficile* was comparable to that of metronidazole and vancomycin. When the antimicrobial activity against EAEC and enterotoxigenic *E. coli* (ETEC) was compared between rifaximin and 6 standard antimicrobial agents, rifaximin had better or comparable activity to most of the agents evaluated, including ampicillin, chloramphenicol, tetracycline, and trimethoprim, consistent with its efficacy in treating travelers' diarrhea.[47]

Alterations in Enteric Bacteria Virulence Factors and Metabolic Products

In studies conducted by Jiang et al., elimination of virulence factors, which would normally allow bacterial attachment to the gastrointestinal lumen and subsequent toxin secretion, was demonstrated at sub-inhibitory concentrations of rifaximin (i.e., concentrations that allowed bacterial viability), thus indicating a potential mechanism for the clinical efficacy in conditions related to bacterial virulence in the GI tract, such as IBS.[53,55] The virulence factors examined were heat-stable, heat-labile, and heat stable/heat labile toxins, coli surface antigen (adhesion) factors 2, 3, and 6, and matrix metalloproteinase.

Studies conducted by Maccaferri et al. assessed the effect of rifaximin on the human gut microbiota using an in vitro human colonic model system with the fecal microbiota of four patients with colon-active Crohn's disease.[54] Rifaximin (at concentrations selected to simulate an 1800 mg/day dosing regimen) did not affect the overall composition of gut microbiota; however, it resulted in increased concentrations of *Bifidobacterium, Atopobium* and *Faecalibacterium prausnitzii,* species that are thought to play beneficial roles in gut homeostasis via anti-inflammatory and immunomodulatory activities. In addition, rifaximin caused a shift in microbial metabolism; short-chain fatty acids were increased and ethanol, methanol, and glutamate production was decreased. Increases in short-chain fatty acid production may benefit the host intestinal mucosa by providing an energy source and promoting epithelial cell growth. Increases in the short-chain fatty acids propanol and decanol may have beneficial effects given that these compounds are decreased in GI diseases as *C. difficile* and *Campylobacter jejuni* infections and

ulcerative colitis. Significant anti-genotoxic effects against hydrogen peroxide were observed in the presence of rifaximin, which the authors attributed to increases in Bifidobacteria. While this is a limited, ex vivo study, its results are promising and further study of the effects of rifaximin on gut flora is warranted.

Reduction of Host-Bacterial Adhesion and Internalization to Intestinal Epithelium

Rifaximin reduced adherence and internalization of bacteria in human cells in a study reported by Brown et al.[55] When human epithelial cell lines were pretreated with rifaximin prior to addition of EAEC to the incubation, EAEC adherence was reduced significantly as compared with control, rifampin, or doxycycline for three of the four cell lines. Furthermore, the attachment and internalization of *Bacillus anthracis* into A549 or HeLa cells were reduced by rifaximin pretreatment, while *Shigella sonnei* attachment and internalization were not affected by rifaximin pretreatment. These potentially therapeutic effects of rifaximin on bacterial adhesion and internalization may be specific to certain bacterial attachment and host cell internalization mechanisms.

Reduction of Host Inflammatory Cytokine Release

Rifaximin inhibited inflammatory cytokine release in human HEp-2 cells.[55] The cytokines examined (GM-CSF, MIP4, MIP5, MMP3, RANTES, TFG-β, IFN-γ, TNFRI, TNFRII, VCAM-1, VEGF, IL-4, IL-6, IL-8, IL-12, AND IL-15) were present in untreated and doxycycline treated cells and all of these cytokines, except MIP5, were detected in rifampin-treated cells. In cells treated with rifaximin, however, only RANTES and IL-4 were detected, with the other 14 cytokines below detectable levels. These differences suggest that rifaximin may have beneficial anti-inflammatory effects on host cells independent of its effects on bacteria and different from the effects of its chemical analog rifampin.

Elimination of Toxin-Mediated Plasmids

Plasmid stability and transmission in Gram-positive and Gram-negative bacterial strains cultured in the presence of sub- and supra-inhibitory concentrations of rifaximin were evaluated.[52] Rifaximin cured all host strains tested of their plasmids, not only under standard experimental conditions but also during spontaneous selection of resistant strains. Furthermore, the presence of rifaximin during conjugation produced a 100-fold reduction in the transfer of genetic material. These data suggest that rifaximin is capable of limiting the transfer of antibiotic-resistance plasmids and the diffusion of virulence factors.

Up-Regulation of Host Cell Detoxification Mechanisms

Multiple studies demonstrate that rifaximin up-regulates detoxification mechanisms in the gastrointestinal lumen, an effect that may result in an enhanced host defense against GI dysbiosis. In PXR-humanized mice, rifaximin significantly induced intestinal PXR, a nuclear receptor that regulates detoxification genes.[58] In contrast, there was no effect on liver PXR in these rifaximin-treated mice.[58] These data are consistent with the known distribution of rifaximin, specifically its limited systemic exposure and high concentration in the intestinal lumen. Consistent with the in vivo mouse data, cell-based reporter gene assays revealed rifaximin-mediated activation of human PXR.[57] These results are consistent with data from studies conducted by Salix, in which rifaximin

incubation in an in vitro human cell system resulted in increased expression of PXR target genes.[59]

In a second study in a mouse model of inflammatory bowel disease, rifaximin ameliorated clinical signs of colitis (body weight change, diarrhea, rectal bleeding, and histology) in PXR-humanized, but not PXR-null mice.[62] In addition, rifaximin treatment resulted in higher survival rates and recovery from colitis signs in PXR-humanized, but not PXR-null mice.

Rifaximin induced the expression of PXR in primary colon epithelial cells; furthermore, reduced expression of PXR by exposure to TNFα was prevented by rifaximin co-treatment.[56] Finally, rifaximin treatment of ex vivo colon biopsies from ulcerative colitis patients activated PXR and increased expression of PXR-regulated detoxification genes. The authors concluded that these non-antibiotic effects of rifaximin could protect the integrity of intestinal barriers against products generated by luminal bacteria.

One of the genes whose expression is regulated by PXR is P-gp. P-gp expression and function in the GI tract has been credited with serving as a defense mechanism in host interactions with GI tract bacteria. In the GI tract, P-gp expression generally is highest in ileal epithelial cells and declines proximally to the jejunum, duodenum, and stomach, with variable colonic expression. In a study conducted in a human in vitro cell model, P-gp mRNA content was increased nine-fold in the presence of 5 μM rifaximin as a result of PXR activation.[59] Based on rifaximin solubility, 5 μM rifaximin is the predicted GI lumen concentration following dosing with the 550 mg tablet.

In humans, reduced MDR1 expression and/or function is observed in UC patients compared with healthy controls.[61,138] While the link has not been established for IBS, these data suggest that up-regulation of PXR detoxification genes in the GI lumen, including induction of P-gp expression, could be beneficial in improving symptoms for patients who experience inflammation due to GI microbial dysbiosis.

Taken as a whole, these data suggest that rifaximin's role as a gut-specific human PXR ligand may result in enhanced intestinal detoxification mechanisms, thereby providing beneficial effects against toxins, including bacterial products, at the intestinal epithelium.

4.2. Microbiologic Resistance

While data exists suggesting that the risk of developing resistance with rifaximin is low compared with systemic antibiotics, Salix is working with the FDA to further study the potential development of bacterial resistance in post-marketing HE studies.

The low risk during rifaximin therapy is thought to be related to studies indicating that resistance to rifaximin is not plasmid-mediated but instead requires a stable mutation in host cell DNA; therefore, dissemination of resistance and cross-resistance to other antibiotics by plasmid-based mechanisms would be eliminated.

The mechanism of bacterial resistance to the rifamycin class of drugs has been particularly well studied since the 1970s and is primarily due to mutations in the chromosomal gene encoding the beta subunit of DNA-dependent RNA Polymerase (RPOB). The mutations are known to occur at highest frequency in two specific loci of the RPOB gene and result in a resistant but sub-optimally functioning enzyme.[139,140,141,142,143,144]

Fitness of Rifamycin-resistant Bacteria

While rifamycin-resistant bacteria are viable, they show major reductions in "fitness" with significant reductions in replication capacity due to corresponding decrements in gene transcription efficiency.[145] In addition to reduced replication capacity, rif-mutants can express reduced virulence profiles as evidenced by a median 1000-fold reduction in sporulation frequency observed in a series of *B. subtilis* rif-mutants.[146] In this way, rif-mutants resemble the profile of bacteria exposed to sub-lethal concentrations of rifaximin where expression of virulence factors required for pathogenesis is lost in the absence of loss of viability.[53] In addition, recent findings by Debbia et al. have shown that rifaximin-resistant E. coli as well as E.coli exposed to sub-lethal doses of rifaximin show similar frequencies of plasmid elimination and increased sensitivity to secondary antibiotic treatments.[52]

These findings indicate that enteric bacteria with acquired resistance to the rifamycin class of antibiotics, and to rifaximin in particular, are more benign than virulent wild-type bacteria. In the presence of a large number of competing bacteria, as is found in the GI tract, the rifaximin-resistant strain would not maintain a competitive advantage (due to its lower fitness level) and should therefore be eliminated, once the antibiotic pressure is removed. This suggests that of all the possible antibiotics that could be used to treat a GI pathology in a large patient population, rifaximin would appear to be the most suitable.

The profile of rifaximin-resistant bacteria elucidated from in vitro studies appears to be borne out in the clinical setting. Mutation to resistance to rifaximin following exposure to high levels of the drug occurs in approximately 1×10^{-7} to 1×10^{-8} exposed bacteria, with some variation seen between bacterial species.[73,52,147] *C. difficile* showed a low incidence of spontaneous mutation to resistance of $< 1 \times 10^{-9}$ exposed bacteria.[73] The selected resistant mutants exhibited rifaximin resistance levels at concentrations ≥ 256 mg/L. The resistance was quite stable without reversion to parental strain susceptibility, suggesting the presence of chromosomal mutations.[147]

The acquisition of resistant coliform or enterococcal colonic flora was monitored in subjects given 3 days, 7 days or 14 days of rifaximin. In the first of the studies, there was a slight (non-statistically significant) increase in rifaximin- or rifampin-resistant coliform flora after three days of rifaximin treatment.[148] In the second study, in which rifaximin was given for two weeks, the rifaximin MIC_{50} and MIC_{90} for coliform and enterococcal fecal flora showed a non-significant one-dilution increase in the rifaximin-treated subjects compared with the placebo-treated subjects.[51] While resistance of the gut flora can occur during rifaximin treatment, one study documenting the occurrence of resistance of fecal flora during rifaximin treatment provided evidence that the resistance was quickly lost when the drug was stopped.[149]

Extra-intestinal Resistance to Rifaximin or Cross-resistance to Rifampin

One important clinical consideration regarding rifaximin resistance is the possibility of producing cross resistance to the related drug, rifampin. Rifampin's value as an antibiotic in infectious diseases lies primarily in its treatment of tuberculosis. In the treatment of tuberculosis, rifampin is not used as a single agent, but is combined with other antitubercular antibiotics to lessen the likelihood of clinically significant resistance. Potential for producing rifampin-resistant strains of *Mycobacterium tuberculosis* by exposure to rifaximin has been studied. Growing *M. tuberculosis* on media containing rifaximin did not select for rifampin-resistant mutants and rifaximin

administration to *M. tuberculosis* infected guinea pigs does not lead to the emergence of rifampin-resistant strains of tuberculosis.[150,151]

Rifampin has been used infrequently as a second-line drug in the treatment of some infections caused by *Staphylococcus aureus*. Two studies have examined the potential relationship between rifaximin treatment and development of resistance in *Staphylococcus* strains. In a study conducted by Valentin et al., rifampin resistance was seen in 2% of staphylococci strains (of which two strains were *S. aureus*) 1 and 9 weeks after discontinuation of rifaximin, not during or on completion of therapy.[152] Extensive research on gut flora after up to 14 days of rifaximin treatment has shown no more than a one-dilution change in susceptibility of the bacteria studied, indicating that there was no major development of resistance.[153]

The likelihood of extra-intestinal bacterial resistance should be diminished with rifaximin treatment due to its intra-luminal activity and low levels of absorption, two factors that reduce the selective pressure for development of resistance. The mechanism for the development of resistance to rifaximin is a chromosomal 1-step alteration in the drug target, DNA dependent RNA polymerase. This mechanism differs from the plasmid-mediated resistance that is easily acquired by susceptible bacteria rendering them resistant to aminoglycosides, sulfonamides, and macrolides. In 2 clinical studies, there was a rapid return from rifaximin-resistant to -sensitive bacterial strains, especially in aerobic species, after rifaximin treatment ended.[149,154] The lack of clinical resistance to rifaximin's efficacy has also been shown in the treatment of SIBO/IBS in a trial in which 3 treatment cycles were used successfully.[155]

4.3. Clinical Pharmacology

4.3.1. Pharmacokinetics

The unique pharmacokinetic properties of rifaximin, namely its poor oral absorption, low systemic exposure in both healthy individuals and those with IBS, and high concentration in the gut lumen following oral administration, contribute favorably to its efficacy and safety profiles.

4.3.2. Pharmacodynamics

Across two studies, rifaximin has demonstrated statistically significant efficacy and approximately linear dose response in eradicating SIBO as reflected by glucose hydrogen breath test (GBT) results.[74,75] In the first study, 90 patients with positive GBT results were randomized to three treatment groups: rifaximin 600 mg/day, rifaximin 800 mg/day, and rifaximin 1200 mg/day for 7 days.[74] In the second study, SIBO patients (n = 80) were randomized to receive rifaximin at doses of 1200 mg/day or 1600 mg/day.[75] GBT normalization rates for rifaximin doses of 600, 800, and 1200 mg/day were 17%, 27%, and 60%, respectively. In the second study, normalization rates at rifaximin doses of 1200 mg/day and 1600 mg/day were 58% and 80%, respectively. The maximum response was observed with a 1600 mg daily dose, similar to the dose tested in TARGET 1 and TARGET 2 (1650 mg daily dose).

4.3.3. Absorption

Rifaximin's gut-specific activity is a direct result of poor oral absorption, resulting in the majority of the dose residing in the GI tract lumen. Following a single 400 mg ^{14}C-rifaximin dose in healthy subjects, > 99.7% of the total radioactive dose recovered was in feces, almost entirely as

unchanged drug; 0.32% of the dose was in urine.[156] In addition, rifaximin showed very low apical→basolateral permeability in Caco-2 cells in vitro.[66]

Systemic exposure of rifaximin following oral administration is low regardless of dose, disease state, or feeding state. Administration of a single 550-mg tablet to fasted and fed healthy subjects resulted in mean $AUC_{0-\infty}$ values of 11.1 ng·h/mL and 22.5 ng·h/mL, respectively. Multiple-dose BID or TID regimens in healthy subjects resulted in mean AUC values of 12.3 ng·h/mL (AUC_{tau}, steady-state), and 9.3 ng·h/mL (AUC_{tau}, steady-state), respectively.[65]

4.3.3.1. Pharmacokinetics - IBS Subjects Versus Healthy Volunteers

Systemic rifaximin exposure is low in subjects with non-C IBS; following repeat dosing of rifaximin 550 mg TID, mean steady-state AUC_{tau} was 16.0 ng·h/mL and mean steady-state maximum concentration (C_{max}) was 4.22 ng/mL.[64]

As shown in Table 5, single-dose pharmacokinetic parameters in subjects with non-C IBS were generally comparable to healthy volunteers. While C_{max}, and AUC values after the multiple-dose regimen were approximately 1.7-fold higher in the non-C IBS subjects, this difference is not considered to be clinically significant given the low exposure in subjects with IBS. Therefore, no dose adjustment is recommended in IBS patients.

Rifaximin pharmacokinetics were found to be linear upon multiple dosing in subjects with IBS, as measured by comparison of single-dose oral clearance (CL/F) and multiple-dose CL/F. Additionally, both IBS subjects and healthy volunteers reached steady-state rifaximin plasma concentrations by Day 2 of multiple dosing with 550 mg tablets TID.

Table 5 Mean (± SD) Plasma Pharmacokinetic Parameters of Rifaximin 550 mg TID in IBS Subjects (RFPK1010) and Healthy Volunteers (RFPK1007)

	RFPK1010 - non-constipation IBS		RFPK1007 - healthy volunteers	
Rifaximin parameters	**Single-Dose (Day 1) N = 24**	**Multiple-Dose TID (Day 14) N=24**	**Single-Dose (Day 1) N = 12**	**Multiple-Dose TID (Day 14) N=14**
C_{max} (ng/mL)	3.49 (1.36)	4.22 (2.66)	4.04 (1.51)	2.39 (1.28)
C_{min} (ng/mL)	not calculated	1.16 (0.877)	not calculated	0.513 (0.359)
T_{max} (h) [a]	0.775 (0-2.00)	1.00 (0.500-2.00)	0.75 (0.50-2.05)	1.00 (0.50-2.03)
AUC_{0-t} (ng·h/mL)	9.29 (4.50)	19.7 (12.6)	8.83 (3.45)	11.6 (5.07)
AUC_{tau} (ng·h/mL)	9.69 (4.16)	16.0 (9.59)	10.4 (3.47)	9.30 (2.70)
$AUC_{0-\infty}$ (ng·h/mL)	15.5 (6.73)	not calculated	11.1 (4.15)	not calculated
CL/F (L/min)	745 (415)	701 (293)	959 (411)	1060 (304)
Rc	not calculated	1.77 (0.836)	not calculated	not calculated
$t_{½}$ (h)[b]	3.14 (1.71)	6.08 (1.68)	1.83 (1.38)	5.63 (5.27)

Source: RFPK1010 and RFPK1007 study reports.
a median (minimum – maximum).
b Data are presented as harmonic mean (pseudo SD).
AUC_{0-t} = area under the concentration-time curve from time 0 (predose) to the last quantifiable concentration-time point; AUC_{tau} = AUC from time 0 (predose) to the end of the dosing interval (8 hours); $AUC_{0-\infty}$ = AUC from time 0 (predose) to infinity; C_{max} = maximum concentration; C_{min} = minimum concentration; Rc = accumulation ratio; T_{max} = time to C_{max}; $t_{½}$ = terminal half-life; CL/F = oral clearance.

4.3.3.2. Efflux Transport Studies

An in vitro study of the permeability of rifaximin across Caco-2 cells (GI cells grown in cell culture) demonstrated low permeability in the apical to basolateral (absorptive) direction and high permeability in the basolateral to apical (efflux) direction.[66] Net permeability was minimal, approximately 1×10^{-6} cm/second, providing evidence that the low systemic exposure of rifaximin in humans after oral administration is driven primarily by its limited translocation across the intestinal wall.

The data from experiments in Caco-2 cells further suggest that rifaximin is a substrate of 1 or more efflux transporters, including P-gp and that P-gp is actively excreting rifaximin into the lumen of the gastrointestinal tract. Experiments with Caco-2 cells also showed that rifaximin was not a strong inhibitor of P-gp activity; minimal inhibition was observed at 50 µM.[157] Additionally, rifaximin was a weak inhibitor (IC_{50} = 83 µM) of human bile salt export protein,[158] the primary transporter regulating ATP-dependent bile salt translocation from the liver to the bile.

Since rifaximin concentrations in the GI tract may reach a theoretical maximum of 5 µM after an oral dose of 550 mg, rifaximin is expected to have minimal inhibitory effects on P-gp transport of other substrates in vivo.

4.3.4. Distribution

Animal pharmacokinetic studies have demonstrated that 80% - 90% of orally administered rifaximin is unabsorbed and remains within the GI lumen until excreted into the feces. At 4 hours following a 24 mg/kg oral dose in rats, less than 0.2% of the dose is distributed into the liver and kidney, and less than 0.01% in other tissues.

Results from a scintigraphy study in healthy subjects confirm that the rifaximin is retained primarily in the digestive tract after oral administration.[159] Following a single 200-mg oral dose, the rifaximin tablet rapidly disintegrated in the stomach (within 6 - 23 minutes) after oral administration, and moved through the small intestine within 3.82 - 6.25 hours post dose, and through the colon within 3.94 - 7.28 hours post dose.

Human plasma binding is 68%.[160]

4.3.5. Metabolism and Drug-Drug Interaction

In vitro and in vivo studies indicate that there is minimal risk of clinically significant drug interactions between rifaximin and other compounds. In clinical studies, rifaximin 550 mg TID did not affect the pharmacokinetics of midazolam or an oral contraceptive to a clinically significant extent.[68,69]

4.3.5.1. In Vitro Studies

In vitro metabolic stability and reaction phenotyping studies suggest that hepatic metabolism of rifaximin in humans is mediated by CYP3A4.[161,162]

In an in vitro hepatocyte induction model, rifaximin has been shown to activate PXR resulting in induction of CYP3A4 as well as P-gp. In vivo, this activation of PXR appears to occur only at the level of the GI epithelium which differentiates rifaximin from other members of the rifamycin class which induce PXR systemically. Specifically, induction of PXR target scenes was observed at rifaximin concentrations from 0.005 to 5 µM, but was lower than the dose-dependent induction

observed for rifampin at the same molar concentrations. CYP3A4 mRNA expression was increased approximately 20-fold by rifaximin 5 µM, while the equivalent rifampin concentration resulted in a 46-fold increase in CYP3A4 mRNA. The differences in the potency of rifaximin and rifampin on CYP3A4 in this model are believed to be due to permeability. Effects on P-gp (MDR1) mRNA were similar for the two compounds, with 9- and 12-fold increases in MDR1 mRNA observed following incubation with 5 µM rifaximin and rifampin, respectively. No induction by rifaximin of CYP1A2 and CYP2B6 was observed when compared with positive controls (3-methylcholanthrene for CYP1A2 and phenobarbital for CYP2B6).

Rifaximin, at concentrations up to 50 µM did not significantly inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 (6βT); for CYP3A4 (1OHMDZ), the rifaximin IC_{50} was 25 µM.[163] No time-dependent inhibition of CYP enzymes was observed in vitro. Based on these data, no clinically relevant CYP-mediated drug-drug interactions are anticipated to be caused by rifaximin.

4.3.5.2. In Vivo Studies

In vivo, rifaximin 550 mg TID (IBS dose) for 7 or 14 days resulted in only slightly reduced exposure to midazolam following a single dose.[164] Midazolam geometric mean ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ following 7 days of rifaximin 550 mg TID (test) versus no rifaximin (reference) were 95.3%, 95.5%, and 96.2%, respectively. As the mean change in systemic exposure was ≤ 10%, the data predict that the clinical significance of a rifaximin interaction with CYP3A4-metabolized drugs would be minimal.

In a drug interaction study evaluating rifaximin and oral contraceptives (OCs), rifaximin resulted in only minimal alterations in systemic exposure to the components and metabolites of Ortho Tri-Cyclen Lo®.[70] Rifaximin 550 mg TID (IBS dose) for 7 days resulted in systemic exposure parameters that were quantitatively similar following OC plus rifaximin when compared with OC alone for the analytes ethinyl estradiol (EE), 17-deacetylnorgestimate (NGMN), and norgestrel (NG). Mean C_{max} values were slightly lower after coadministration of OC and rifaximin for the 3 analytes. While the clinical relevance of the minimal C_{max} (EE, NGMN, NG) and AUC (NG) reductions in the presence of rifaximin is not known, altered efficacy of OCs containing EE and norgestimate is not expected during concomitant administration with rifaximin.

4.3.6. Excretion

After a single oral 400 mg dose of ^{14}C-labeled rifaximin in healthy subjects, 96.94% of the total radioactive dose was recovered; 0.32% of the dose was excreted in the urine, and 96.62% of the radioactivity was excreted in feces (almost entirely as unchanged drug).[156]

There are low concentrations of rifaximin in human bile following oral administration. In a study in cholecystectomy patients receiving multiple rifaximin doses, bile concentrations were too low for quantitation in 7 of the 13 subjects; in the remaining 6, the median bile concentration was 6.4 µg/mL.[165] In bile duct cannulated rats, approximately 1.1% of an oral ^{14}C-rifaximin dose was excreted in the bile. The rate of systemic clearance by metabolism, as predicted by human liver microsomes and human hepatocytes in vitro, is low (< 30% of hepatic blood flow in microsomes, and no detectable turnover in hepatocytes), suggesting that rifaximin metabolic clearance is limited by hepatocellular permeability.

4.3.7. Dose Selection in TARGET 1 and TARGET 2

The dose and dosing regimen used in TARGET 1 and TARGET 2 were based on clinical response, GI transit, and glucose breath test normalization data. Analysis of daily IBS symptoms in the Phase 2 study RFIB2001 showed superiority in improvement in bloating, abdominal pain, and sense of urgency in the 1100 mg BID dose group versus placebo, suggesting that doses higher than 550 mg BID were effective. The results of a scintigraphy study, RFPK1002, indicated that mean intestinal transit time of a rifaximin tablet was 4.47 ± 2 hours; given this transit time, a TID regimen would maintain rifaximin exposure in the small intestine over the majority of the day, which could be needed for significant effects on gut flora metabolism and host epithelial response.[159]

The TID regimen was further supported by results from published studies showing statistically significant efficacy for rifaximin in IBS patients utilizing TID treatment (400 mg TID).[39,77] Results from dose-ranging studies for rifaximin in SIBO (described in Section 4.3.2) showed increasing efficacy in symptoms similar to those observed in IBS at progressively higher doses using TID treatment, along with linear dose response in glucose breath test normalization, providing further support for both a higher daily dose and TID treatment.

5. Overview of the Completed Clinical Development Program for IBS

The studies performed by Salix for rifaximin in the treatment of non-C IBS are presented Table 6. Published studies by Pimentel, Sharara, and others initially described the effectiveness of rifaximin in the treatment of IBS and related symptoms.[39,77] These studies provided a scientific basis for the Salix development program, which began with the dose-ranging, phase 2b study RFIB2001. Results from RFIB2001 confirmed findings in the literature and guided the design of the phase 3 TARGET studies. The two TARGET studies confirmed the treatment benefit for rifaximin in non-C IBS patients by demonstrating statistically significant and clinically meaningful relief of IBS symptoms and a favorable safety profile.

Table 6 Table of Completed Salix Clinical Studies

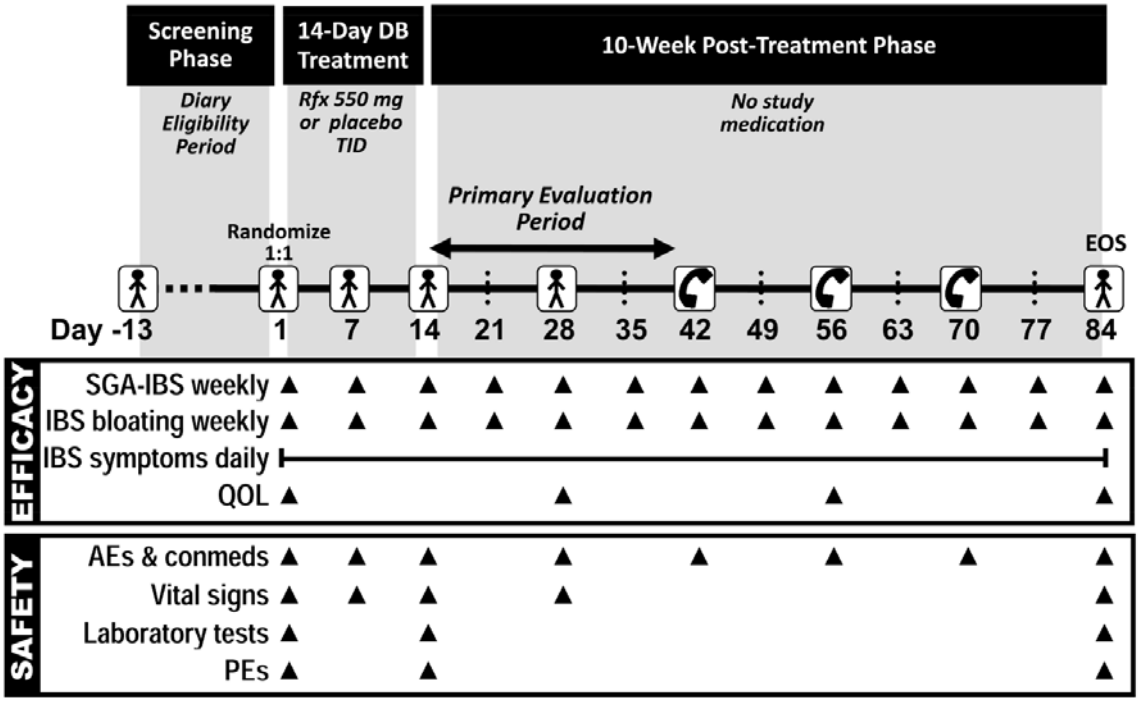
Study	Study Design Rifaximin Dose Regimen/ Control Dose Regimen (Number of Subjects)	Duration	Subject Population
TARGET 1 (RFIB3007)	Double-blind, placebo-controlled, phase 3 study • Rifaximin 550 mg TID (N=309) • Placebo TID (N=314)	14 days of treatment; 10 weeks of follow-up	non-C IBS patients, confirmed using Rome II
TARGET 2 (RFIB3008)	Double-blind, placebo-controlled, phase 3 study • Rifaximin 550 mg TID (N=315) • Placebo TID (N=320)	14 days of treatment; 10 weeks of follow-up	non-C IBS patients, confirmed using Rome II
RFIB2001	Double-blind, placebo-controlled, phase 2b study • Rifaximin 275 mg BID (N=95) • Rifaximin 550 mg BID for 2 weeks (N=191) • Rifaximin 550 mg BID for 4 weeks (N=98) • Rifaximin 550 mg tablet x 2 BID (N=99) • Placebo BID (N=197)	14-28 days of treatment; 12 weeks of follow-up	IBS-D patients, confirmed using Rome II

Abbreviations: IBS = irritable bowel syndrome; non-C IBS = non-constipation IBS; TID = 3 times a day; IBS-D = diarrhea-predominant IBS; and BID = twice a day

5.1. TARGET 1 and TARGET 2 Study Design

The phase 3 confirmatory TARGET studies were identically-designed, randomized, double-blind, placebo-controlled, 12-week studies (see Figure 7). Participating subjects were randomized in a 1:1 ratio to receive either rifaximin 550 mg TID or placebo TID. Subjects received study drug during a 2-week treatment phase, and were followed in a 10-week post-treatment phase.

Figure 7 Study Design for TARGET 1 and TARGET 2



Abbreviations: AE = adverse event; Conmeds = concomitant medications; EOS = end-of-study; IBS = irritable bowel syndrome; PE = physical exam; QoL = quality of life; RFX = rifaximin; SGA = Subject Global Assessment; SGA-IBS = Subject Global Assessment of IBS symptoms (i.e., global IBS symptoms); TID = 3 times daily.

The rifaximin dose regimen and treatment duration for phase 3 (550 mg TID for 14 days) was selected based on considerations from phase 2, pharmacokinetic and scintigraphic study data, the published literature, and consultations with thought leaders in IBS. While the co-primary endpoints in the phase 2 RFIB2001 study showed positive results for rifaximin in a 550 mg BID dose, additional data suggested that a higher daily dose and a TID regimen would be even more effective and beneficial to IBS patients. The 12 week duration for phase 3 included a 2-week treatment period and 10 weeks of post-treatment follow-up. Efficacy findings from phase 2 and the published literature showed that sustained clinical benefit with rifaximin was not dependent on continuous treatment. Rifaximin's treatment benefit in these studies was sustained during follow-up periods of up to 16 weeks following 10 to 14 days of treatment.[39,77] Comparison of 2 week and 4 week treatment regimens with rifaximin 550 mg BID in RFIB2001 also showed no added benefit for a treatment regimen beyond 2 weeks. Given the potential for rifaximin to work in part via induction of PXR-targeted detoxification gene products, two weeks was also estimated as the time needed to allow gene up-regulation effects to reach steady-state. Based on these findings a 2 week treatment period was selected for the phase 3 studies. The 10-week follow-up was selected in accordance with FDA recommendations for evaluating rifaximin in IBS.

5.1.1. Subject Population (TARGET 1 & TARGET 2)

The phase 3 studies enrolled IBS subjects using Rome II criteria with active diarrhea and without constipation during the ≥ 7-day diary eligibility phase. In addition, subjects had undergone a colonoscopy within the last 2 years as part of an evaluation for IBS or IBS symptoms (which excluded inflammatory or neoplastic disease). The Rome II criteria were the most widely used

criteria in the clinical setting for diagnosing and subtyping IBS.[89,90,91] Methods for diagnosing and subtyping IBS using Rome II are presented below in Table 7.

All subjects in the TARGET studies exhibited characteristics of IBS-D without constipation at baseline, and were therefore considered to have had non-C IBS. To ensure that subjects with constipation symptoms at baseline were excluded, subjects were ineligible if they presented with the following symptoms of IBS-C during screening: < 3 bowel movements per week; hard or lumpy stools; and straining during a bowel movement.

Study subjects in phase 3 were also considered to have had mild-to-moderate IBS. During screening the following average daily symptom scores for IBS symptoms were required for entry into the study:

- Abdominal pain and discomfort average score of 2 through 4.5;
- Bloating average score of 2 through 4.5; and
- Stool consistency score of at least 3.5.

Average symptom scores for abdominal pain and bloating were derived from a 7-point Likert scale (0=not at all; 1=hardly; 2=somewhat; 3=moderately; 4=a good deal; 5=a great deal; 6=a very great deal) and a daily 'how bothersome was your symptom' question. Stool consistency was measured on a 5 point scale (1=very hard; 2=hard; 3=formed; 4=loose; or 5=watery).

The baseline severity criteria allowed for the inclusion of a balanced range of IBS symptom severity in the studies, with only subjects with very mild or very severe IBS symptoms excluded. The selected symptom severity criteria were chosen based on response patterns observed in RFIB2001, and to eliminate factors that could confound the outcome (e.g., floor/ceiling effects, the inclusion of severe patients with serious co-morbidities or conditions that were not IBS).

Table 7 Rome II: IBS Diagnosis and Subtyping

Rome II Criteria	
At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain associated with 2 or more of the following: • Relieved with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool	
Rome II Subtyping	
Symptoms: 1. Fewer than 3 bowel movements a week 2. More than 3 bowel movements a day 3. Hard or lumpy stools 4. Loose (mushy) or watery stools 5. Straining during a bowel movement 6. Urgency (having to rush to have a bowel movement) 7. Feeling of incomplete bowel movement 8. Passing mucus (white material) during a bowel movement 9. Abdominal fullness, bloating, or swelling	
Diarrhea-predominant IBS:	One or more of 2, 4, or 6, and none of 1, 3, or 5; Or, 2 or more of 2, 4, or 6, and 1 of 1 or 5 (hard or lumpy stools do not qualify).
Constipation-predominant IBS:	One or more of 1, 3, or 5, and none of 2, 4, or 6; Or, 2 or more of 1, 3, or 5, and 1 of 2, 4, or 6.
Alternating IBS:	The alternating presence of the two above conditions

References: Ersryd et al.,[89] Corazziari et al.[90] and Thompson et al.[91]

5.1.2. Efficacy Endpoints (TARGET 1 & TARGET 2)

Efficacy endpoints in the TARGET studies were based on subject responses to weekly questions regarding their global IBS symptoms and IBS bloating, and responses to symptom-specific daily efficacy measures for global IBS symptoms, IBS bloating, IBS abdominal pain and discomfort, stool consistency, stool frequency, and urgency to defecate. Subjects recorded their daily and weekly IBS symptoms into an interactive voice response system (IVRS) for the efficacy analyses.

Efficacy assessments were collected over the full 12 weeks of subject observation. The primary and key secondary endpoints were measured in the PEP (i.e., Weeks 3 to 6, or the first 4 weeks following treatment cessation), the primary analysis time point. Monthly responder endpoints were also performed which evaluated efficacy for rifaximin in IBS symptoms over the entire 3 months of observation.

5.1.2.1. Primary Endpoint and Key Secondary Endpoint (TARGET 1 & TARGET 2)

The primary endpoint was the proportion of subjects who achieved adequate relief of global IBS symptoms during the PEP. Adequate relief of global IBS symptoms was defined as a response of "yes" to the following weekly SGA question for at least 2 of 4 weeks in the PEP: *"In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms? [Yes/No]"*. The key secondary endpoint, adequate relief of bloating, was assessed during the PEP (2 of 4 weeks) using a similar weekly question for bloating.

Agreement on these endpoints was reached with the FDA at the EOP2 meeting (December 2007), and these endpoints were consistent with over 20 years of clinical experience in IBS.

5.1.2.2. Secondary Endpoints - Daily Assessments of IBS Symptoms (TARGET 1 & TARGET 2)

Daily assessments of symptom severity were collected over 12 weeks in phase 3 to provide independent substantiation of findings from the weekly assessments. For global IBS symptoms, bloating, and abdominal pain, daily symptom severity was assessed using a 'how bothersome was your symptom' question with a 7-point Likert scale. Assessments for other IBS symptoms used symptom-specific daily measures.

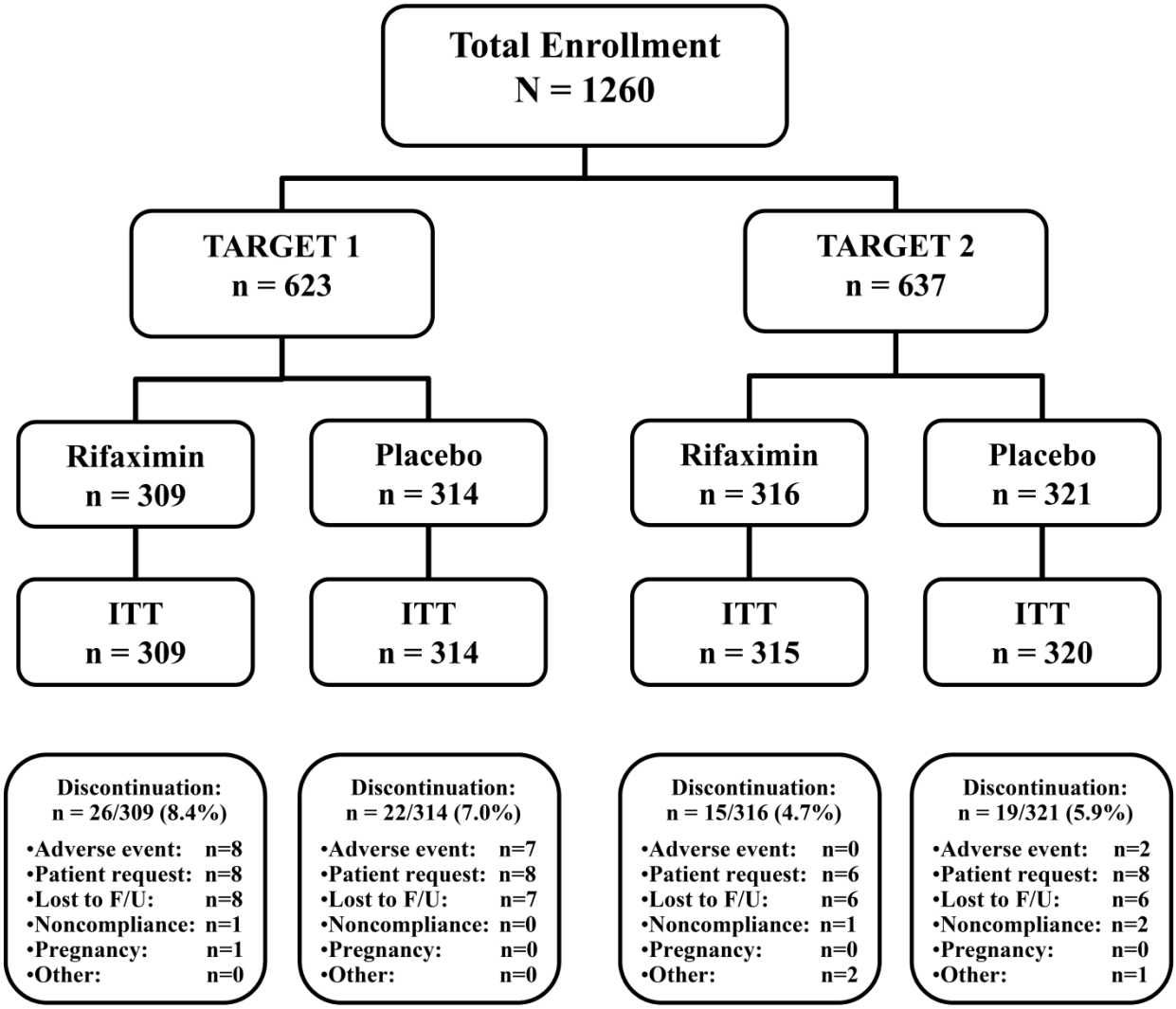
5.1.2.3. FDA Abdominal Pain and Stool Consistency Endpoint (TARGET 1 & TARGET 2)

At the pre-NDA meeting (December 2009), the FDA acknowledged prior concurrence with Salix on the pre-specified primary and key secondary endpoints for phase 3. In addition, the FDA requested an additional analysis for a new endpoint. This exploratory endpoint includes abdominal pain responders (defined as ≥ 30% decrease from baseline in abdominal pain) <u>and</u> stool consistency responders (defined as stool consistency score of < 4, [indicating formed stools]). As discussed with the FDA, subjects were responders for abdominal pain <u>and</u> stool consistency if they reached responder criteria for BOTH abdominal pain AND stool consistency ≥ 2 weeks during the PEP (Weeks 3 through 6). This endpoint is consistent with the endpoint in the draft FDA guidance for IBS studies.

5.1.3. Subject Disposition in Phase 3 (TARGET 1 & TARGET 2)

A total of 1260 subjects were randomized in a 1:1 ratio to rifaximin 550 mg TID or placebo in the TARGET studies (Figure 8). The study completion rate was > 90% in both studies. Similar proportions of rifaximin and placebo subjects discontinued early, and there were no notable between-group differences in the reasons for early discontinuation.

Figure 8 Subject Disposition for TARGET 1 & TARGET 2



Source: TARGET 1 & 2 Study Data

5.1.4. Demographics and Baseline Characteristics in Phase 3 (TARGET 1 & TARGET 2)

Demographic and baseline characteristics are summarized for TARGET 1 and TARGET 2 in Table 8. The phase 3 studies enrolled IBS subjects confirmed using the validated Rome II criteria with active diarrhea and without constipation during the ≥ 7-day diary eligibility phase. Demographic characteristics were similar for subjects across studies and treatment groups. In each study, the mean age of subjects was approximately 46 years. Most subjects were white (> 89% of each group), and the majority were female (≥ 70% of each group). These findings were consistent with trends for demographic characteristics for IBS patients in the US.

Each treatment group had comparable IBS histories and similar average daily symptom scores at baseline. All IBS subjects were subtyped as IBS-D at baseline using Rome II. Mean daily scores for global IBS symptoms, IBS bloating, and IBS abdominal pain were all > 3 and similar for rifaximin- and placebo-treated subjects. These scores were based on 7-point Likert scales (range: 0 to 6), with higher scores indicating more severe symptoms. The mean daily score for stool consistency was 3.9 for each treatment group using a 5-point scale (1 [very hard] to 5 [watery]), and each group averaged ~ 3 bowel movements per day at baseline. In both studies, subjects felt urgency associated with > 80% of their bowel movements.

Table 8 Demographics and Baseline Characteristics for TARGET 1 & 2 (ITT Population)

	TARGET 1		TARGET 2	
	Rifaximin 550 mg TID (N=309)	**Placebo (N=314)**	**Rifaximin 550 mg TID (N=315)**	**Placebo (N=320)**
Age – yr Mean (SD)	46.2 (15.0)	45.5 (14.6)	45.9 (13.9)	46.3 (14.6)
Gender n (%)				
Female	235 (76)	222 (71)	227 (72)	225 (70)
Male	74 (24)	92 (29)	88 (28)	95 (30)
Race n (%)				
White	281 (91)	280 (89)	282 (90)	302 (94)
Black	24 (8)	30 (10)	21 (7)	14 (14)
Other	4 (1)	4 (1)	12 (4)	4 (1)
IBS Subtype (Rome II)				
IBS-D	309 (100)	314 (100)	315 (100)	320 (100)
IBS-C	0	0	0	0
IBS-A	0	0	0	0
Average Daily Scores Mean (SD)				
IBS symptoms[a,d]	3.4 (0.7)	3.4 (0.7)	3.4 (0.7)	3.4 (0.7)
Bloating[b,d]	3.3 (0.8)	3.3 (0.7)	3.2 (0.7)	3.3 (0.7)
Abdominal pain and discomfort[c,d]	3.3 (0.7)	3.2 (0.7)	3.3 (0.7)	3.3 (0.7)
Stool consistency[e]	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)
Average daily bowel movements				
Mean (SD)	2.9 (1.3)	3.0 (1.4)	3.0 (1.6)	3.0 (1.5)
Percentage of days with stool urgency[f]				
Mean (SD)	81.8 (22.3)	82.9 (22.3)	81.3 (22.8)	82.2 (22.5)
Duration of IBS symptoms[g]- yr				
Mean (SD)	11. 9 (10.5)	11.4 (11.9)	10.8 (10.2)	11.8 (10.4)

Abbreviations: ITT = intent-to-treat; TID = three times daily; SD = standard deviation; IBS = irritable bowel syndrome; IBS-D = diarrhea-predominant IBS; IBS-C = constipation-predominant IBS; and IBS-A = alternating IBS

a The question asked was 'In Regards to all your symptoms of IBS; on a scale of 0-6, how bothersome were your symptoms of IBS today?'

b The question asked was 'In Regards to your specific IBS symptom of bloating; on a scale of 0-6, how bothersome was your IBS-related bloating today?'.

c The question asked was 'In Regards to your specific IBS symptom of abdominal pain and discomfort; on a scale of 0-6, how bothersome were your IBS-related abdominal pain and discomfort today?'.

d Responses were: 0=not at all, 1=hardly, 2= somewhat, 3=moderately, 4=a good deal, 5=a great deal, 6=a very great deal.

e Responses to the question 'What was the overall stool form of your bowel movements today?' were 1 = very hard, 2 = hard, 3 = formed, 4 = loose, 5 = watery.

f Calculated as 100*(# days with urgency with any of the bowel movements / number of days with bowel movements).

g Calculated as (date ICF signed - date of first experience of IBS)/365.25.

5.2. RFIB2001 (Phase 2b)

5.2.1. Study Design (RFIB2001)

Study RFIB2001 was a phase 2b, double-blind, placebo-controlled study of 4 rifaximin dosing regimens (3 rifaximin doses) in subjects with IBS. The primary objective was to evaluate the efficacy of the14-day course of oral rifaximin at 550 mg BID versus placebo in providing adequate relief of IBS symptoms. Secondary objectives included analysis of 2 weeks vs. 4 weeks of rifaximin treatment, and analysis of the duration of subject response over a 12-week post-treatment phase.

Subjects were randomized to receive daily doses of the following treatment regimens: placebo BID, rifaximin 275 mg BID, rifaximin 550 mg BID, or rifaximin 1100 mg BID for 2 weeks. These 4 groups subsequently received an additional 2 weeks of placebo for a total of 4 weeks of treatment. A fifth group of subjects received rifaximin 550 mg BID for a period of 4 weeks. Subjects who successfully responded to treatment at the end of a 28-day Treatment Phase were followed in a 12-week Post-Treatment Phase.

There were 2 co-primary measures of efficacy for the RFIB2001 study: adequate relief of global IBS symptoms and adequate relief of bloating. The primary analysis compared the 550 mg BID rifaximin group versus placebo. Other efficacy analyses evaluated IBS symptoms (e.g., abdominal pain, stool consistency) using daily assessment tools.

5.2.2. Subject Disposition, Demographics, and Baseline Characteristics (RFIB2001)

A total of 680 subjects were randomized and entered the Treatment Phase of the RFIB2001 study. For the primary efficacy analyses, 191 subjects were randomized to the rifaximin 550 mg BID 2 week group and 197 subjects were randomized to the placebo group. The remaining subjects received one of the other rifaximin dosing regimens: 275 mg BID (N=95), 550 mg BID for 4 weeks (N=98), or 1100 mg BID (N=99). Most subjects (90%) completed the treatment phase, and 249 subjects entered the post-treatment, follow-up phase. Similar proportions of rifaximin and placebo subjects discontinued the studies early, and there were no notable between-group differences in the reasons for early discontinuation.

Demographic characteristics for subjects in RFIB2001 were similar to those observed in the TARGET studies. In the intent-to-treat (ITT) population, median age was 46 years, most subjects were white (93%), and the majority were female (75%). Baseline IBS characteristics were also similar in RFIB2001 and the phase 3 trials. Randomized subjects had IBS confirmed by Rome II criteria, and most subjects (> 85%) had IBS-D at baseline. The mean number of bowel movements per day at baseline was 3.4, and the mean rating for being bothered by abdominal pain/discomfort or bloating was 3.4 for each treatment group, using a 7-point Likert scale (range: 0 to 6), with higher scores indicating more severe symptoms. Baseline IBS symptoms were comparable among the 4 rifaximin treatment groups and the placebo group.

6. Clinical Efficacy

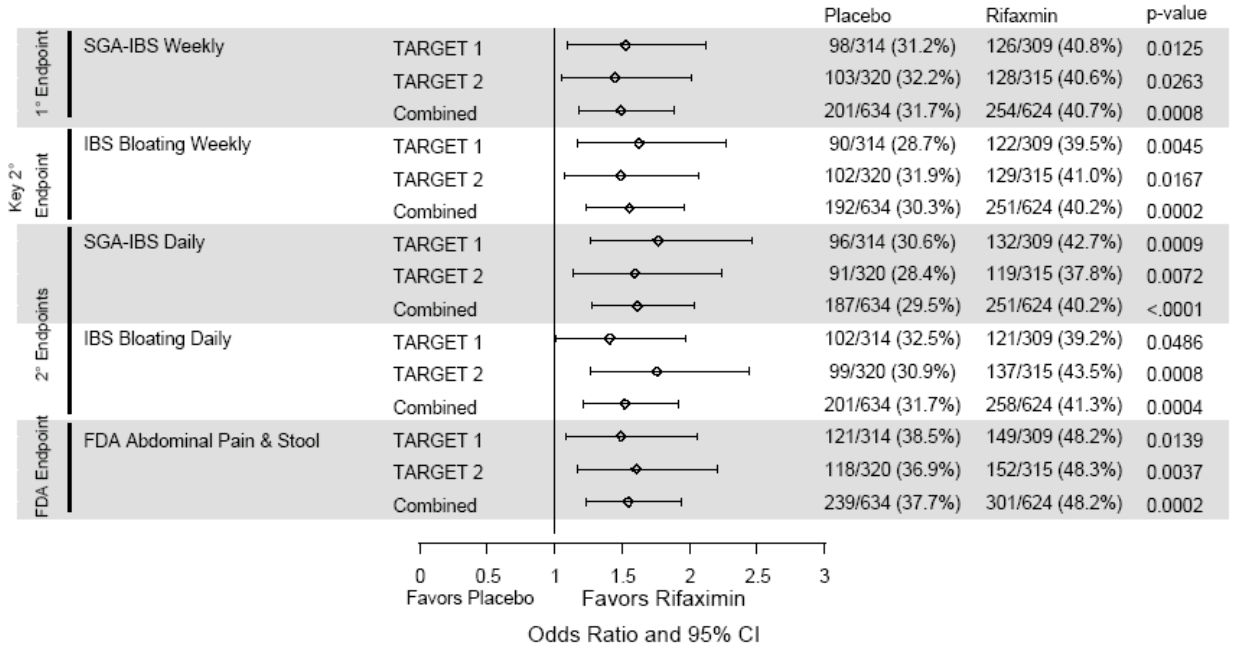
The clinical efficacy of rifaximin in the treatment of non-C IBS is supported by the totality of evidence from clinical studies in phase 1, 2, and 3 and several published reports.[46,39,77] The primary clinical efficacy evidence comes from 2 pivotal, identically-designed, double-blind, placebo-controlled, phase 3 studies (TARGET 1 and TARGET 2). Full results of the TARGET studies have been disclosed previously in a peer-reviewed scientific journal.[46]

6.1. Overview of Key Efficacy Results in TARGET 1 & TARGET 2

Primary Evaluation Period (Weeks 3-6): Rifaximin demonstrated efficacy in the treatment of non-C IBS based on statistically significant symptom relief versus placebo for the primary endpoint, which was defined as adequate relief at Weeks 3-6 (PEP):

- **Primary Endpoint:** TARGET 1 and TARGET 2 each met the pre-specified primary endpoint. Significantly more rifaximin patients had adequate relief of their global IBS symptoms over the 1 month following treatment based on weekly subject global assessments (SGA); (TARGET 1: 41% vs. 31%, p = 0.0125; TARGET 2: 41% vs. 32%, p = 0.0263; Figure 9).
- **Key Secondary Endpoint:** Significantly more rifaximin patients had adequate relief of their IBS-related bloating over the 1 month following treatment based on weekly SGA; (TARGET 1: 40% vs. 29%, p = 0.0045; TARGET 2: 41% vs. 32%, p = 0.0167; Figure 9).
- **FDA Draft Guidance Endpoint:** Significantly more rifaximin patients were responders in each trial for abdominal pain AND stool consistency (TARGET 1: 48% vs. 39%, p = 0.0139; TARGET 2: 48% vs. 37%, p = 0.0037; Figure 9).
- **Additional Secondary Endpoints:** Consistency of results was reflected in daily ratings of global IBS symptoms and IBS bloating (Figure 9).

Figure 9 Relief of IBS Symptoms during the PEP (Weeks 3-6) – TARGET 1 & TARGET 2

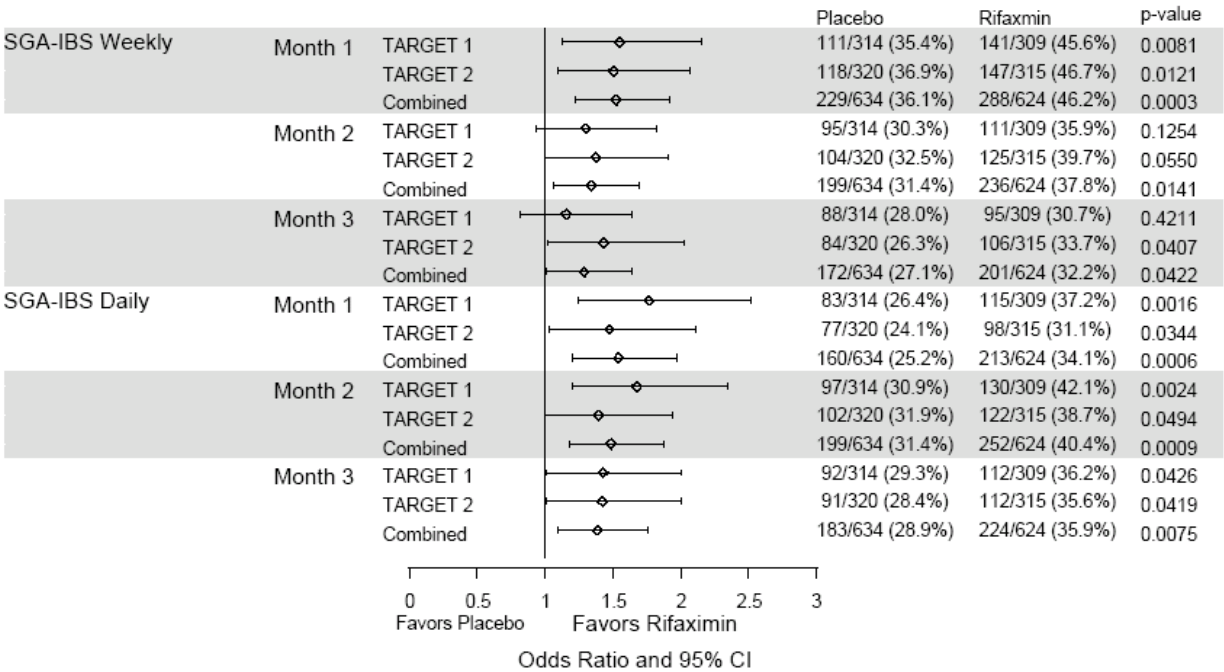


Source: TARGET 1 & 2 study data. This figure shows the percentage of responders by treatment group, and odds ratios for the likelihood of being a responder for the key study endpoints in the PEP (Weeks 3-6). P-values and odds ratio were obtained using the logistic regression model with fixed effects for treatment arm, analysis center, and study (combined data only).

Efficacy Over Time: In the TARGET studies, rifaximin 550 mg TID demonstrated early onset of relief and persistent efficacy for IBS symptom relief following a single 2-week course of treatment.

- **Onset of Relief**: Rifaximin was associated with a significantly earlier time to response compared with placebo for global IBS symptoms, IBS bloating, and for the abdominal pain AND stool consistency endpoint from the draft FDA guidance (see Section 6.2.3.1).
- **Point Prevalence:** Rifaximin subjects were consistently more likely to experience adequate relief of global IBS symptoms at each independent month (i.e., Month 1, 2, or 3 isolated) during the TARGET studies, as measured by weekly or daily data (Figure 10). TARGET 1 and TARGET 2 were each powered to show significant differences at Weeks 3-6 (PEP) only. For purposes of providing a more precise estimated treatment effect for these additional analyses, the combined data are presented below.

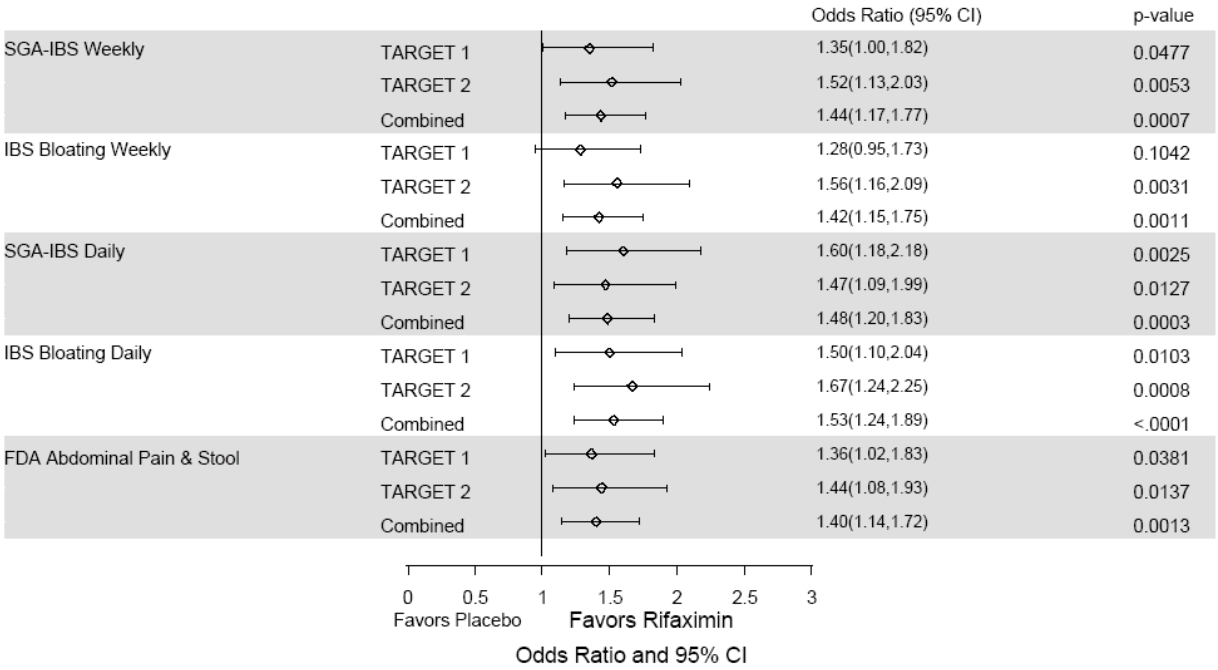
Figure 10 Global IBS Symptoms Responders at Each Month, Based on Weekly and Daily Measures in TARGET 1 and TARGET 2 (Point Prevalence Analysis)



Source: TARGET 1 & 2 study data. P-values and odds ratio were obtained using the logistic regression model with fixed effects for treatment arm, analysis center, and study (combined data only).

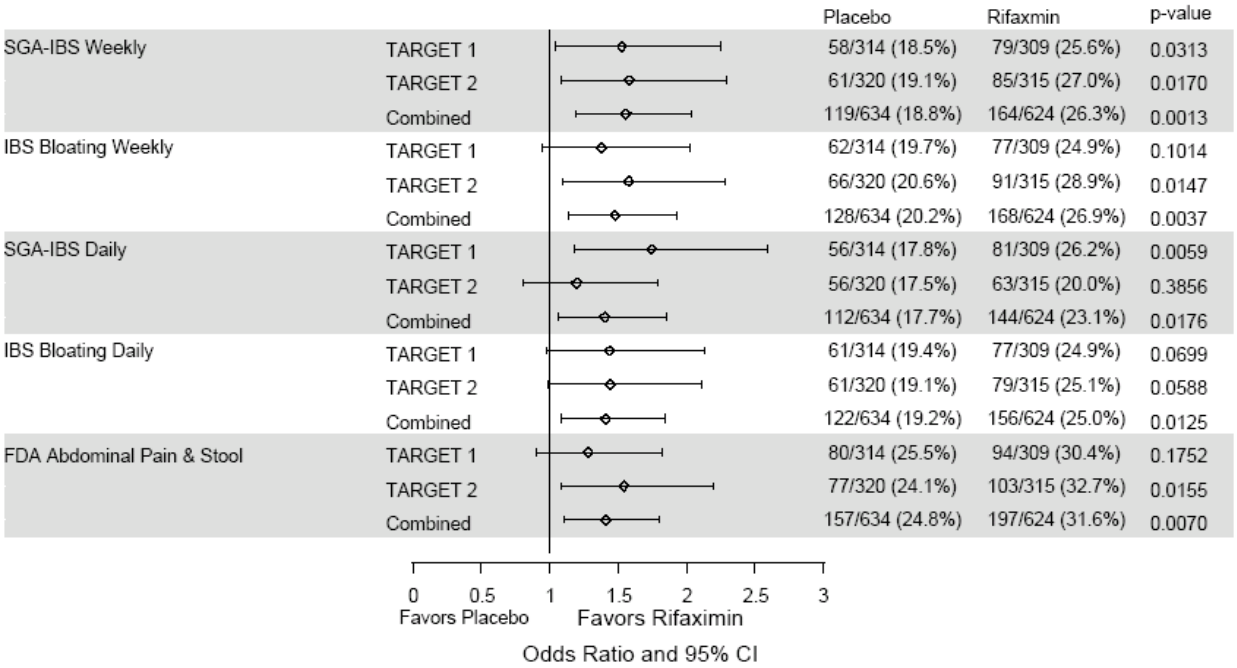
- **Persistent Efficacy**: Persistent efficacy for the entire 12 weeks was analyzed based on monthly data at Weeks 4, 8, and 12 and was defined as the number of months that subjects achieved adequate relief during the entire 3 months of the study. As shown in Figure 11, odds ratios from the number of months analyses demonstrate that rifaximin subjects were significantly more likely to experience more months of response for IBS symptoms, IBS bloating, and for abdominal pain AND stool consistency (FDA draft endpoint) compared with placebo over the entire 3 months of observation. Persistent efficacy was also analyzed using these endpoints in a more stringent analysis of responders for all 3 months of observation. As shown in Figure 12, rifaximin subjects were more likely to be responders in each endpoint for all 3 months of observation, demonstrating the robustness of rifaximin's persistent treatment effect.

Figure 11 Impact of Rifaximin on Relief of IBS Symptoms Over 3 Months in the TARGET Studies – Number of Months Analysis



Source: TARGET 1 & 2 study data. This figure shows odds ratios for the likelihood of being a responder for the key study endpoints over the entire 3 months of the study. The outcome variable is the number of months that subjects are responders. P-values and odds ratio were obtained using the proportional odds model for ordinal outcome.

Figure 12 Efficacy Endpoint Responders for the Entire 3 Months of the TARGET Studies



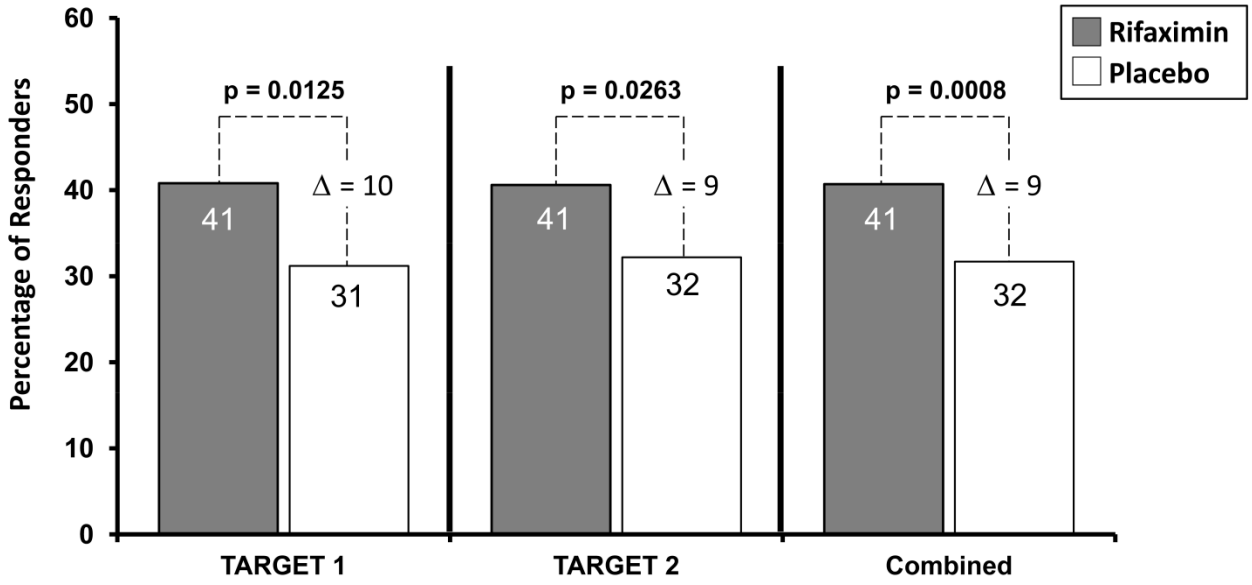
Source: TARGET 1 & 2 study data. This figure shows the percentage of subjects who are responders for all 3 months and odds ratios for the likelihood of being a responder for all 3 months in the key study endpoints during the TARGET studies. P-values and odds ratio were obtained using the logistic model with fixed effects for treatment arm, analysis center, and study (combined data).

6.2. Primary Efficacy Endpoint – Adequate Relief of Global IBS Symptoms

The primary endpoint in the TARGET studies, adequate relief of global IBS symptoms (i.e., SGA-IBS Weekly) at PEP, was experienced by significantly more rifaximin subjects than placebo subjects during the PEP (TARGET 1: 41% vs. 31%, p = 0.0125; TARGET 2: 41% vs. 32%, p = 0.0263; Combined Data: 41% vs. 32%, p = 0.0008; see Figure 13).

The daily assessment endpoint for global IBS symptoms (i.e., SGA-IBS Daily) substantiated the weekly results, with significant between-group differences in favor of rifaximin similar to those obtained for the primary endpoint (TARGET 1: 43% vs. 31%, p = 0.0009; TARGET 2: 38% vs. 28%, p = 0.0072; Combined Data: 40% vs. 30%, p < 0.0001).

Figure 13 Adequate Relief of Global IBS Symptoms (TARGET 1 & 2 and Combined Data)



Source: TARGET 1 & TARGET 2 study reports and Integrated Summary of Efficacy for NDA 21-361
Notes: 1) Adequate relief of global IBS symptoms was defined as a response of "yes" to the following weekly subject global assessment question for at least 2 of 4 weeks in the PEP: "In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms? [Yes/No]".
2) The p-values were obtained from a logistic regression model with fixed effects for treatment arm and analysis center in each study. For the combined data, the p-value was obtained from a logistic regression model with fixed effects for treatment arm, analysis center and study.

6.2.1. Sensitivity Analyses of the Primary Endpoint

For the primary endpoint, three different sensitivity analyses were conducted to address the impact of the missing data on the efficacy outcome. The results of each of the three analyses demonstrated no effect of missing data on the primary efficacy outcome.

Consistent with FDA guidance for IBS trials, the TARGET studies utilized an IVRS to capture patient-reported data for efficacy assessments. Overall, there was a low occurrence of missing data in the IVRS. Because the primary endpoint was defined as at least 2 weeks of relief within a given 4 weeks of response, not all subjects with missing data had insufficient data to determine response. In fact, in most cases non-compliance with completing the questionnaire was limited to

one week in these studies. There was no statistically significant difference in the number of subjects with insufficient data in Target 1 (p=0.5162) and Target 2 (p=0.7288) (see Table 9).

Table 9 Subjects with Missing Data in the PEP – TARGET 1 & TARGET 2

	TARGET 1		TARGET 2	
	Rifaximin (N=309) n (%)	**Placebo (N=314) n (%)**	**Rifaximin (N=315) n (%)**	**Placebo (N=320) n (%)**
Subjects with no missing IVRS entries during the PEP	277 (89.6)	281 (89.5)	291 (92.4)	280 (87.5)
Subjects with any missing IVRS entries during PEP	32 (10.4)	33 (10.5)	24 (7.6)	40 (12.5)
Subjects with sufficient data	10 (3.2)	15 (5.8)	8 (2.5)	21 (6.6)
Subjects with insufficient data	**22 (7.1)**	**18 (5.7)**	**16 (5.1)**	**19 (5.9)**

Source: TARGET 1 & 2 study data. Abbreviations: PEP = primary evaluation period; IVRS = interactive voice response system.

For the primary endpoint, missing data were handled by the principle of last observation carried forward (LOCF), whereby missing values were replaced with the last previous non-missing value. The baseline values were not carried forward. To assess the impact of missing data on efficacy outcomes, three sensitivity analyses were conducted: a worst case analysis method, an observed cases method, and a multiple imputation method. For the worst case method, subjects with missing weekly data were considered to be non-responders for that week. For the observed cases analysis method, subjects who had insufficient data to determine response were excluded. Thus, the observed cases method does not incorporate all randomized subjects. For the multiple imputation method, missing answers in the IVRS were estimated from existing data.

Results using these sensitivity analyses are provided in Table 10 and demonstrate a consistent and significant ($p < 0.05$ for all) rifaximin treatment effect for the primary endpoint in each study. Each statistical test demonstrated that the overall results and conclusions from the primary endpoint were robust and unaffected by analysis method utilized to account for missing data. Therefore, there was no dependence of missing data on the primary efficacy outcome.

Table 10 Adequate Relief of Global IBS Symptoms – Primary and Sensitivity Analyses Responders (TARGET 1 & TARGET 2)

Study Analysis	**Rifaximin 550 mg TID n/N (%)**	**Placebo n/N (%)**	**p-value[a]**
TARGET 1 Responders			
Primary ITT Analysis (LOCF)	126/309 (41)	98/314 (31)	0.0125
Observed Cases Analysis	122/277 (44)	96/281 (34)	0.0158
Worst Case Analysis	126/309 (41)	98/314 (31)	0.0125
Multiple Imputation Analysis	133/309 (43)	103/314 (33)	0.0072
TARGET 2 Responders			
Primary ITT Analysis (LOCF)	128/315 (41)	103/320 (32)	0.0263
Observed Cases Analysis	118/291 (41)	88/280 (31)	0.0232
Worst Case Analysis	123/315 (39)	101/320 (32)	0.0478
Multiple Imputation Analysis	130/315 (41)	105/320 (33)	0.0264

Source: TARGET 1 & 2 study data. Abbreviations: LOCF = last observation carried forward.
a. p-values were obtained from a logistic regression model with fixed effects for treatment arm and analysis center.

6.2.2. Subgroup Analyses of the Primary Endpoint

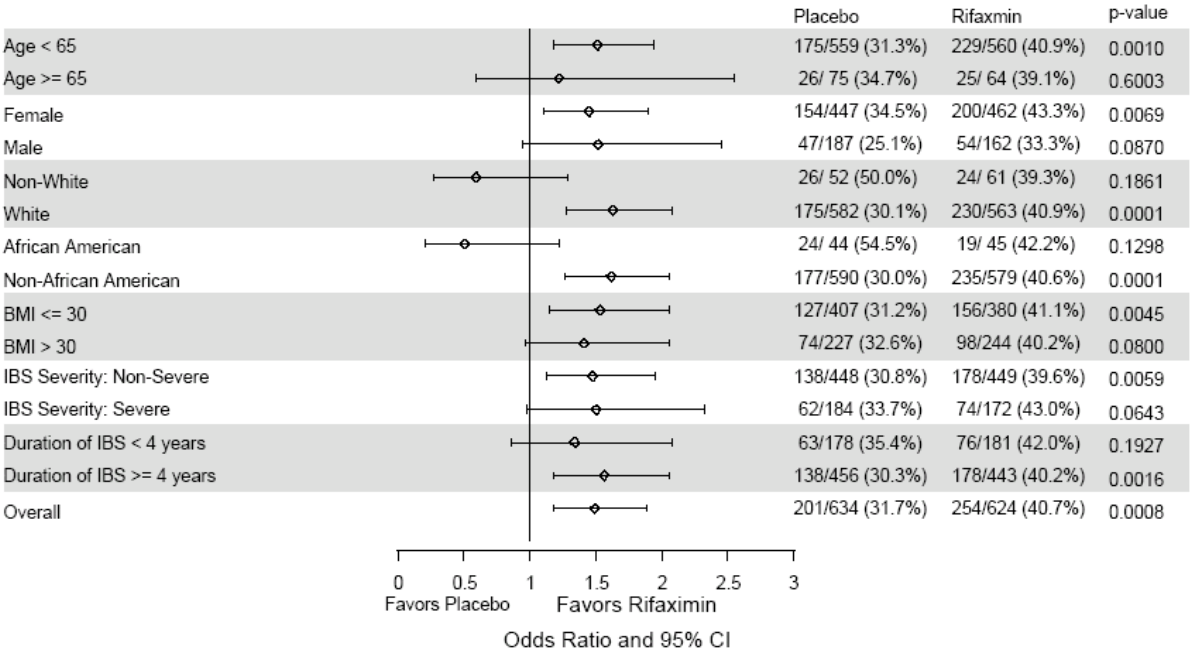
Subgroup analyses of the primary endpoint were conducted by age (< 65 years; ≥ 65 years), gender, race (white, non-white; African American, non-African American), IBS baseline severity (severe; non-severe), body mass index (≤ 30; > 30) and duration of IBS symptoms (< 4 years; ≥ 4 years). Overall, a consistent rifaximin treatment effect was observed across subgroups in the combined data from the TARGET studies for the primary endpoint (Figure 14).

By gender, the percentage of subjects experiencing adequate relief of global IBS symptoms was higher in the rifaximin group compared with the placebo group for both females (43% vs. 35%) and males (33% vs. 25%). The treatment difference was statistically significant for females (p = 0.0069), and a statistical trend was observed in favor of rifaximin for males (p = 0.0870). Consistent with the IBS population in the US, the male subgroup (n = 349) was smaller than the female subgroup (n = 909).

By race, there was a pronounced rifaximin-treatment effect in the subgroup analyses of white subjects (41% vs. 30%, p = 0.0001). However, the reason for the divergent effect seen in the small number of non-white subjects is not known at this time.

Patterns of treatment response by subgroup were similar for analyses of IBS bloating and the FDA-requested endpoint for abdominal pain and stool consistency.

Figure 14 Subgroup Analyses: Adequate Relief of Global IBS Symptoms Responders (ITT Population – TARGET 1 & 2 Combined Data)



Source: TARGET 1 & 2 combined study data. Abbreviations: ITT = intent to treat; and BMI = body mass index.
Note: IBS severity was categorized as severe and non-severe by baseline IBS quality of life [QoL] score. The IBS-QoL scale ranged from 0 (poor) to 100 (maximum QoL). Subjects with a baseline score ≤ 40 were classified as severe.

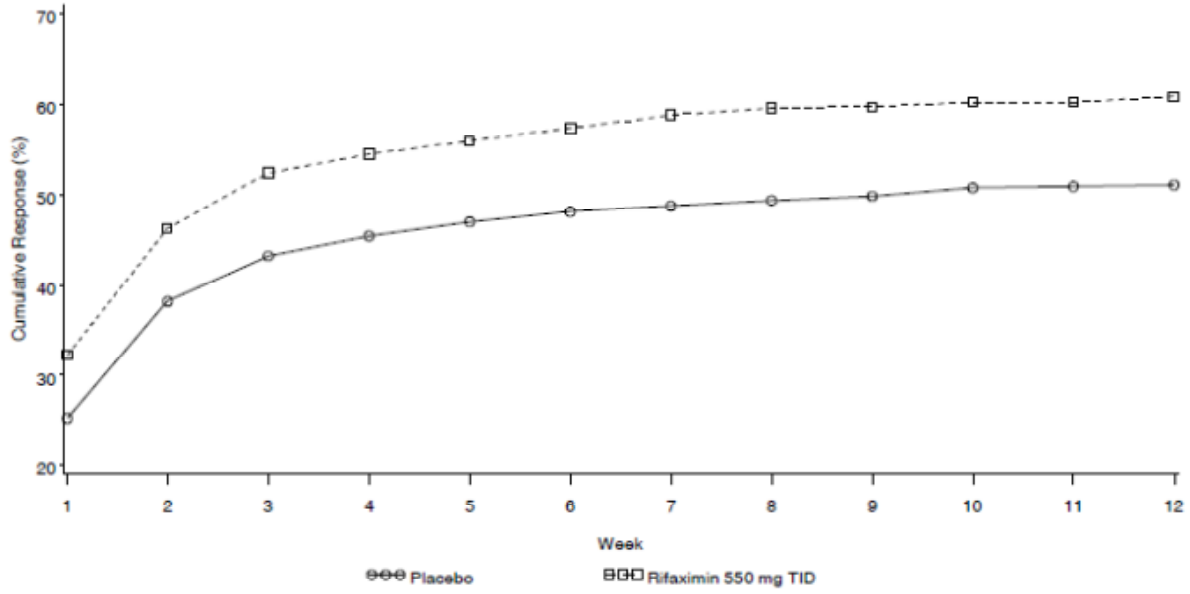
6.2.3. Efficacy Over Time - Adequate Relief of Global IBS Symptoms

6.2.3.1. Onset of Relief

Figure 15 illustrates cumulative response by onset week for the primary efficacy endpoint, where onset refers to the week of first response The therapeutic benefit of rifaximin for adequate relief of global IBS symptoms (as measured by weekly data) was observed early in the TARGET studies and this treatment difference was sustained over 12 weeks. The data from the combined TARGET studies demonstrate a significant difference in the distribution of time to onset of responders in favor of rifaximin 550 mg BID versus placebo (p = 0.0027, from a Kolmogorov-Smirnov test).

Similar trends in distribution of time to onset of responders were observed for the combined TARGET studies in the IBS bloating endpoint (p = 0.0473) and abdominal pain and stool consistency endpoint (p = 0.0036).

Figure 15 Cumulative Response Curve for Adequate Relief of Global IBS Symptoms (Primary Endpoint – TARGET 1 & TARGET 2 Combined Data)



Source: Target 1 & 2 combined study data. This figure show cumulative response by onset week of response.

6.2.3.2. Persistent Efficacy Analyses

Persistent efficacy for adequate relief of global IBS symptoms was analyzed based on monthly data at Weeks 4, 8 and 12, and defined as the number of months that subjects achieved adequate relief of global IBS symptoms during the entire 3 months of the study. As shown in Table 11, rifaximin subjects were significantly more likely to experience more months of adequate relief of global IBS symptoms during the complete 3-month period in TARGET 1 (p = 0.0477), TARGET 2 (p = 0.0053), and in the combined analysis of these studies (p = 0.0007).

Similar trends were observed in the monthly responder analyses for IBS bloating and for abdominal pain and stool consistency (see Figure 11 in Section 6.1).

Table 11 Analysis of Persistent Efficacy: Number of Months of Adequate Relief of Global IBS Symptoms – TARGET 1 & TARGET 2

	TARGET 1		TARGET 2		Combined	
	Rifaximin 550 mg TID N = 309 n (%)	**Placebo N = 314** n (%)	**Rifaximin 550 mg TID N = 315** n (%)	**Placebo N = 320** n (%)	**Rifaximin 550 mg TID N = 624** n (%)	**Placebo N = 634** n (%)
Number of Months of Relief up to Month 3						
0	150 (49)	174 (55)	139 (44)	177 (55)	289 (46)	351 (55)
1	50 (16)	44 (14)	59 (19)	41 (13)	109 (18)	85 (13)
2	30 (10)	38 (12)	32 (10)	41 (13)	62 (10)	79 (13)
3	79 (26)	58 (19)	85 (27)	61 (19)	164 (26)	119 (19)
p-value[a]	p = 0.0477		p = 0.0053		p = 0.0007	

Source: TARGET 1 & TARGET 2 study reports and integrated summary of efficacy for NDA 21-361.
Abbreviations: TID = three times daily.
a The p-value was obtained from the proportional odds model for ordinal outcome.

Persistent efficacy was also analyzed for adequate relief of global IBS symptoms in a more stringent analysis of subjects who were responders for all 3 months. As shown in Table 12, significantly more rifaximin subjects than placebo subjects experienced adequate relief of global IBS symptoms (SGA-IBS weekly) for all 3 months in TARGET 1 (p = 0.0313), TARGET 2 (p = 0.0170), and in the combined analysis of these studies (p = 0.0013).

Similar trends were observed for 3-month responders for IBS bloating and for abdominal pain and stool consistency (see Figure 12 in Section 6.1).

Table 12 Analysis of Persistent Efficacy: Adequate Relief of Global IBS Symptoms Responders for All 3 Months – TARGET 1 & TARGET 2

	TARGET 1		TARGET 2		Combined	
	Rifaximin 550 mg TID N = 309	**Placebo N = 314**	**Rifaximin 550 mg TID N = 315**	**Placebo N = 320**	**Rifaximin 550 mg TID N = 624**	**Placebo N = 634**
Adequate Relief of Global IBS Symptoms for All 3 Months						
n (%)	79 (26)	58 (19)	85 (27)	61 (19)	164 (26)	119 (19)
p-value[a]	p = 0.0313		p = 0.0170		p = 0.0013	

Source: TARGET 1 & TARGET 2 study data
Abbreviations: TID = three times a day.
a The p-value was obtained from the logistic regression model for binary outcome.

6.2.3.3. Adequate Relief of Global IBS Symptoms During Weeks 7 through 12

Efficacy analyses were conducted to evaluate rifaximin's durable treatment effect in the TARGET studies for Weeks 7 through 12 (i.e., the 6 weeks following the PEP) for adequate relief of IBS symptoms. For analysis of these 6 weeks, using all subjects an average treatment effect was calculated by classifying subjects as 'no response during PEP'; 'response during PEP and < 50% response in 6 weeks beyond PEP'; or 'response during PEP and ≥ 50% response in 6 weeks beyond PEP'. This is a rank-based method and results of the analysis using ordered logistic

regression indicate a statistically significant treatment effect for rifaximin in the 6 weeks following the PEP (Table 13).

Salix considered a number of additional statistical approaches, including a conditional analysis using only responders in the PEP. In consultation with outside thought leaders, it was concluded this type of analysis is inconsistent with an intent-to-treat approach. The concern around a conditional analysis approach is the bias which would be introduced because the randomized population is not the same as the conditional analysis population.

Table 13 Average Treatment Effect from Weeks 7 through 12: Global IBS Symptoms – TARGET 1 & TARGET 2

	TARGET 1		TARGET 2		Combined	
	RFX N = 309 n (%)	**Placebo N = 314** n (%)	**RFX N = 315** n (%)	**Placebo N = 320** n (%)	**RFX N = 624** n (%)	**Placebo N = 634** n (%)
Non-responder	183 (59)	216 (69)	187 (59)	217 (68)	370 (59)	433 (68)
Responder & < 50% time	38 (12)	23 (7)	38 (12)	29 (9)	76 (12)	52 (8)
Responder & ≥ 50% time	88 (29)	75 (24)	90 (29)	74 (23)	178 (29)	149 (24)
p-value[a]	p = 0.0239		p = 0.0289		p = 0.0015	

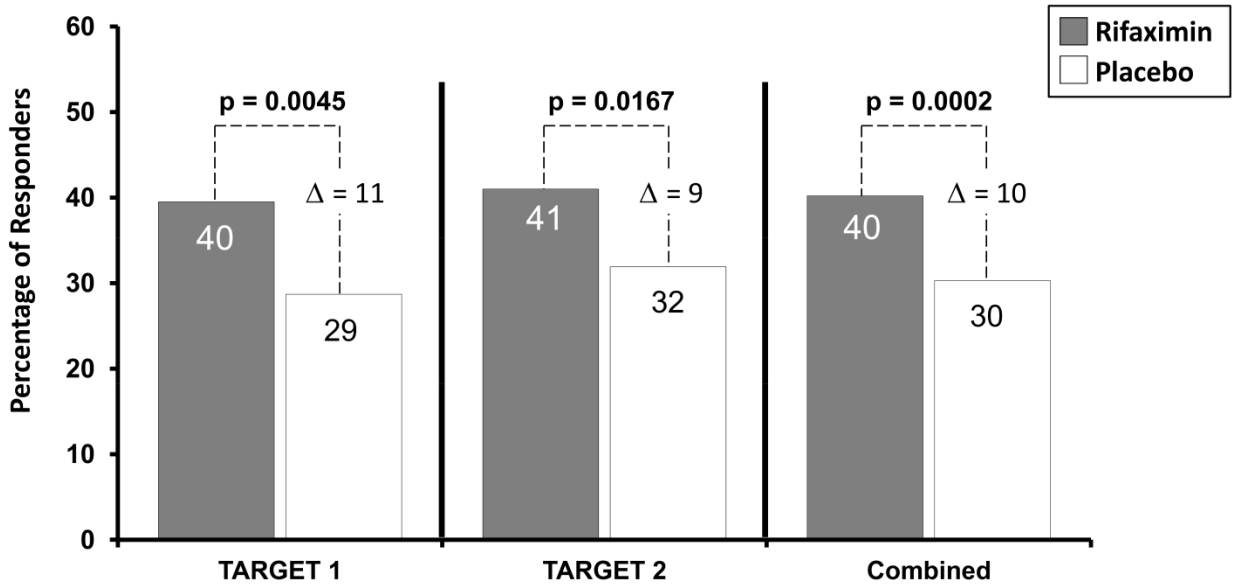
Source: TARGET 1 & TARGET 2 study data
Abbreviations: TID = three times daily; RFX = rifaximin 550 mg TID.
a The p-value was obtained from the proportional odds model for ordinal outcome.

6.3. Key Secondary Endpoint – IBS Bloating

Adequate relief of IBS bloating (key secondary endpoint – IBS bloating weekly) was also experienced by significantly more rifaximin subjects than placebo subjects during the PEP in each study and in combined analysis of the studies (TARGET 1: 40% vs. 29%, p = 0.0045; TARGET 2: 41% vs. 32%, p = 0.0167; Combined Data: 40% vs. 30%, p = 0.0002; Figure 16).

The daily assessment endpoint for IBS bloating substantiated the weekly results with significant between-group differences in favor of rifaximin similar to those for the key secondary endpoint (TARGET 1: 39% vs. 33%, p = 0.0486; TARGET 2: 44% vs. 31%, p = 0.0008; Combined Data: 41% vs. 32%, p = 0.0004).

Figure 16 Adequate Relief of IBS Bloating (TARGET 1 & 2, and Combined Data)



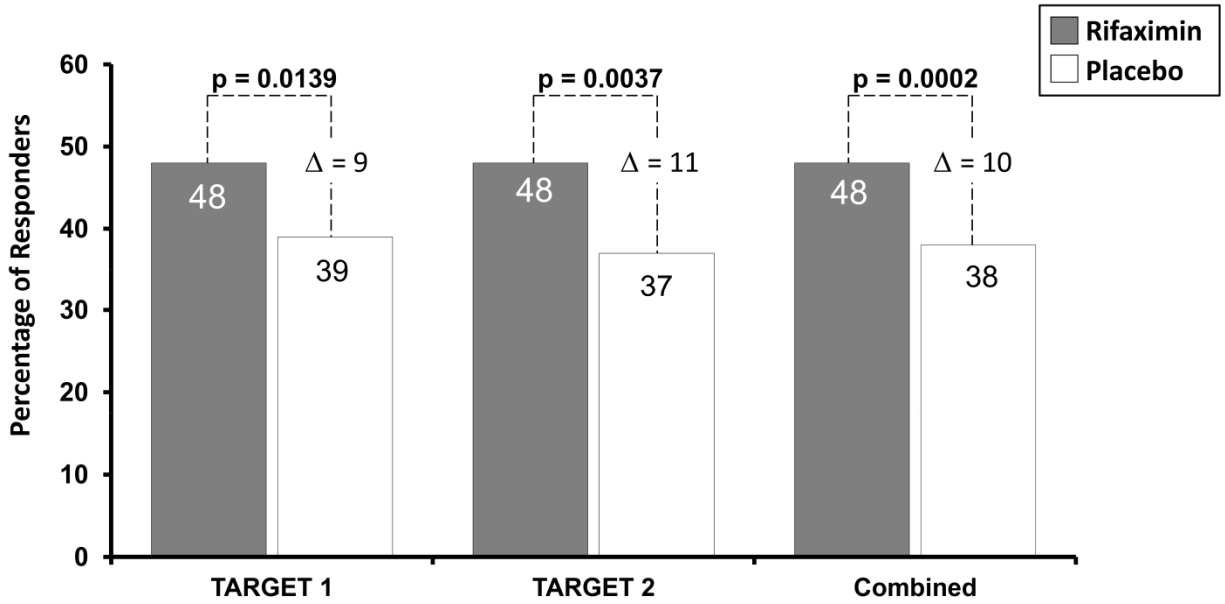
* See legend to Figure 13 for statistical methods. (Note: The key secondary efficacy endpoint for the phase 3 studies was the proportion of subjects who achieved adequate relief of IBS bloating for ≥ 2 of 4 weeks during the PEP.)

6.4. Abdominal Pain and Stool Consistency – FDA Draft Guidance Endpoint

Efficacy data from the TARGET studies were also evaluated in a composite abdominal pain and stool consistency endpoint, consistent with FDA draft guidance. For this endpoint significantly more rifaximin subjects were responders during the PEP compared with placebo subjects in each study and in combined analysis of the studies (see Figure 17). Significantly larger proportions of rifaximin-treated subjects were also responders for the abdominal pain component endpoint (TARGET 1, p = 0.0157; TARGET 2, p = 0.0194) and for the stool consistency component endpoint (TARGET 1, p = 0.0014; TARGET 2, p = 0.0047) in the PEP. These endpoints were based on daily measures of symptom severity. Outcomes for these endpoints were similar to outcomes observed in the primary and key secondary endpoint, demonstrating the robustness of the rifaximin treatment effect in non-C IBS subjects.

The number of months analyses for this composite endpoint were also consistent with results from the primary analyses, with rifaximin-treated subjects more likely to be responders over the entire 3 months of observation versus placebo in TARGET 1 (odds ratio = 1.36, p = 0.0381) and TARGET 2 (odds ratio = 1.44, p = 0.0137).

Figure 17 Abdominal Pain and Stool Consistency Endpoint Responders (TARGET 1 & 2, and Combined Data)



*Subjects were abdominal pain responders if they experienced a ≥ 30% decrease compared with baseline in weekly average abdominal pain score for ≥ 2 weeks in the PEP. Subjects were stool consistency responders if they had a weekly average of stool consistency score < 4 for ≥ 2 weeks in the PEP. Stool consistency was measured on a 5-point daily scale (1 = very hard; 2 = hard; 3 = formed; 4 = loose; or 5 = watery). A score of < 4 was consistent with a formed stool.

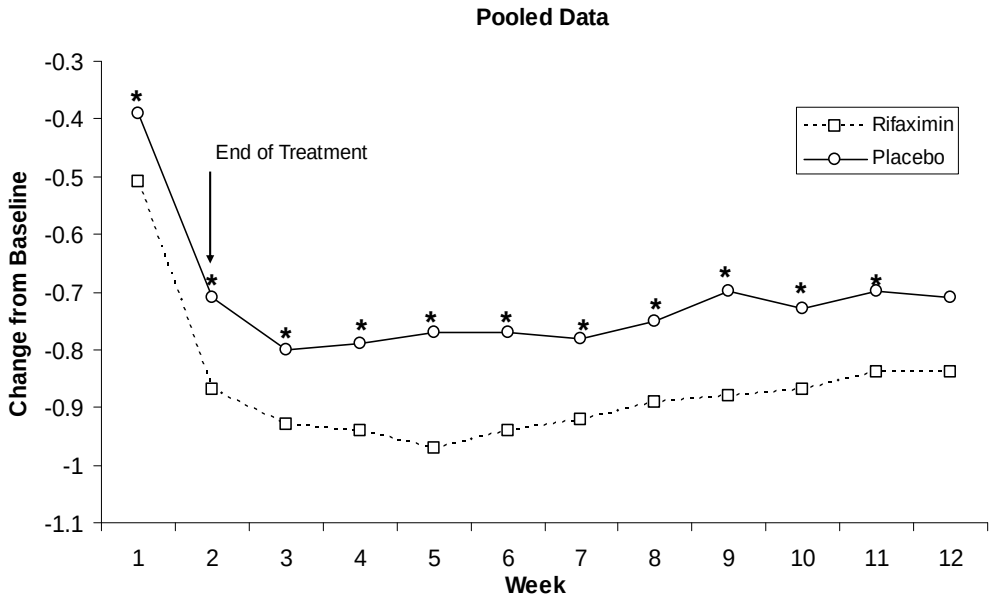
6.5. Rifaximin Impact on Individual IBS Symptoms Over 12 Weeks

The TARGET studies demonstrated that rifaximin subjects had greater improvements in global IBS symptoms, less bloating, less abdominal pain and discomfort, better stool consistency, greater reductions in sense of urgency, and fewer stools per day over 12 weeks of daily assessments.

Figure 18 through Figure 22 illustrate change from baseline in daily IBS symptom scores at each week in the TARGET studies using combined data for the rifaximin and placebo treatment groups. The figures show the mean change from baseline at each week for global IBS symptoms, bloating, abdominal pain, stool urgency, and stool consistency, respectively. Statistically significant differences between treatment groups at any given week are marked in the figures with an asterisk.

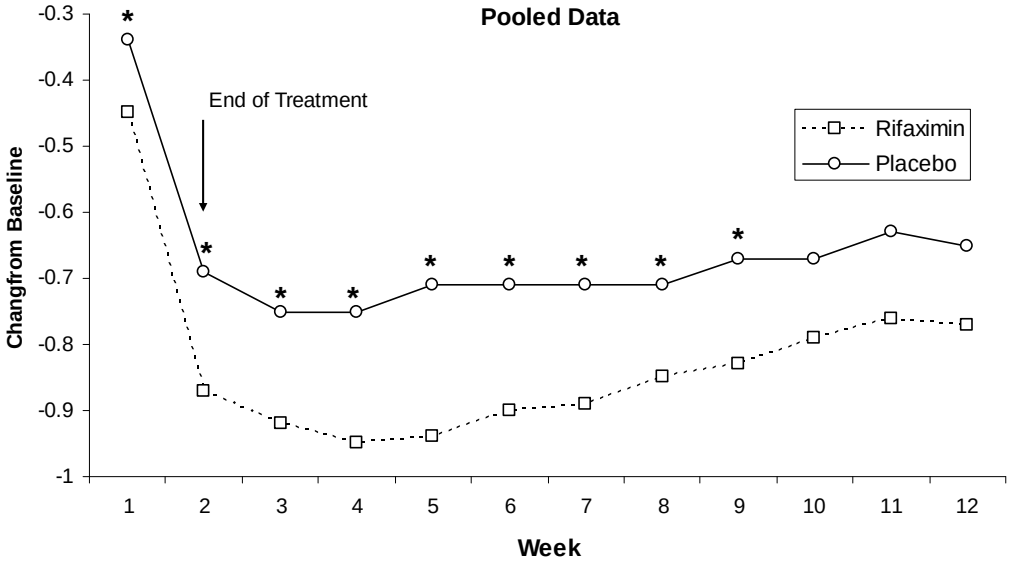
Rifaximin subjects showed larger improvements (i.e., reduced symptom severity) compared with placebo subjects for every symptom analyzed at each of the 12 weeks of study in the combined data. The majority of these between-group differences at each week were statistically significant in favor of rifaximin treatment. Results were similar when each study was analyzed independently. Rifaximin treatment demonstrated greater improvement versus placebo in each of these key clinical IBS symptoms over a 12-week period, with only 2 weeks of treatment.

Figure 18 GLOBAL IBS SYMPTOMS: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 - ITT Population)



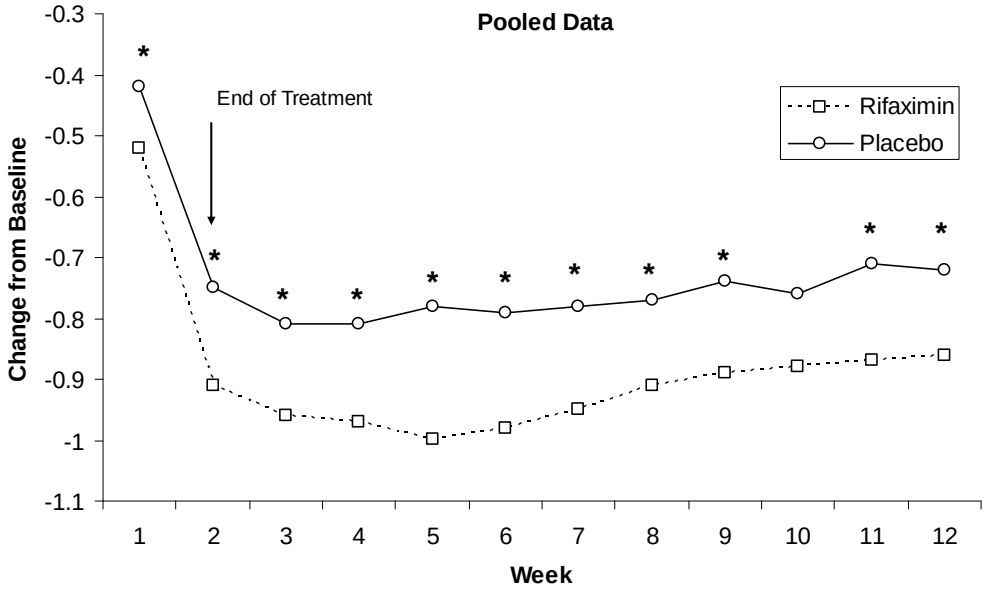
* Represents $p < 0.05$ by linear regression model comparing the LS mean change from baseline between treatment groups adjusting for analysis center, baseline, and baseline by treatment interaction

Figure 19 IBS BLOATING: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 - ITT Population)



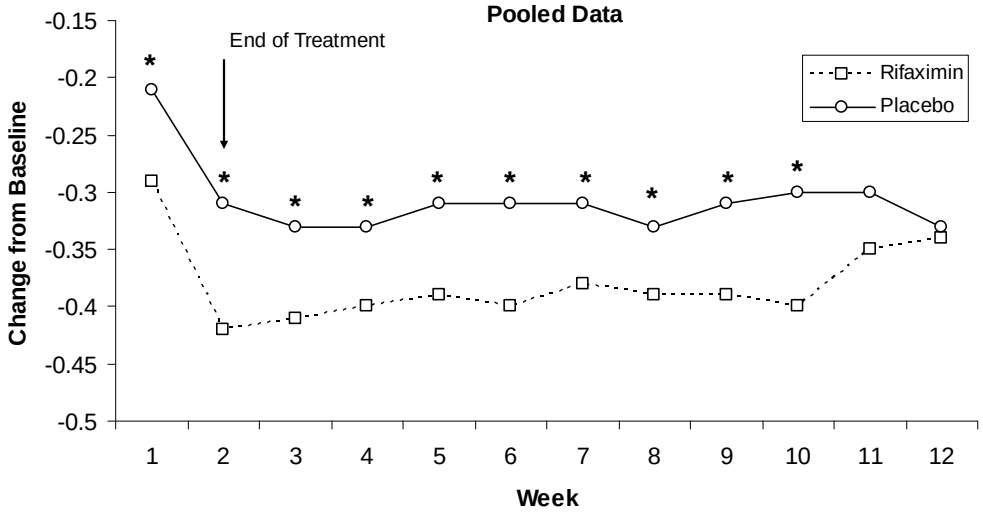
* Represents $p < 0.05$ by linear regression model comparing the LS mean change from baseline between treatment groups adjusting for analysis center, baseline, and baseline by treatment interaction

Figure 20 ABDOMINAL PAIN AND DISCOMFORT: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 - ITT Population)



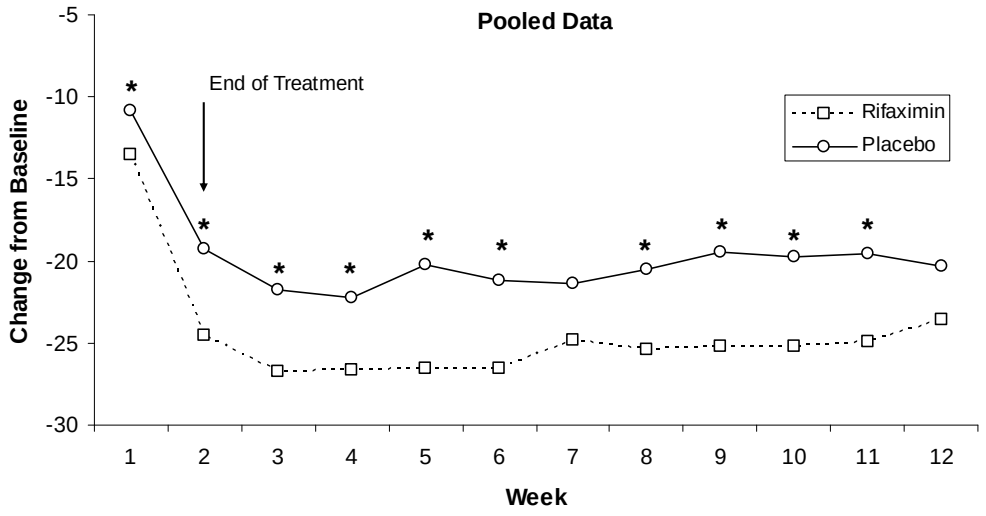
* Represents $p < 0.05$ by linear regression model comparing the LS mean change from baseline between treatment groups adjusting for analysis center, baseline, and baseline by treatment interaction

Figure 21 STOOL CONSISTENCY: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 - ITT Population)



* Represents $p < 0.05$ by linear regression model comparing the LS mean change from baseline between treatment groups adjusting for analysis center, baseline, and baseline by treatment interaction

Figure 22 STOOL URGENCY: Mean Change from Baseline in Average Daily Score (Combined Data from TARGET 1 & TARGET 2 -ITT Population)



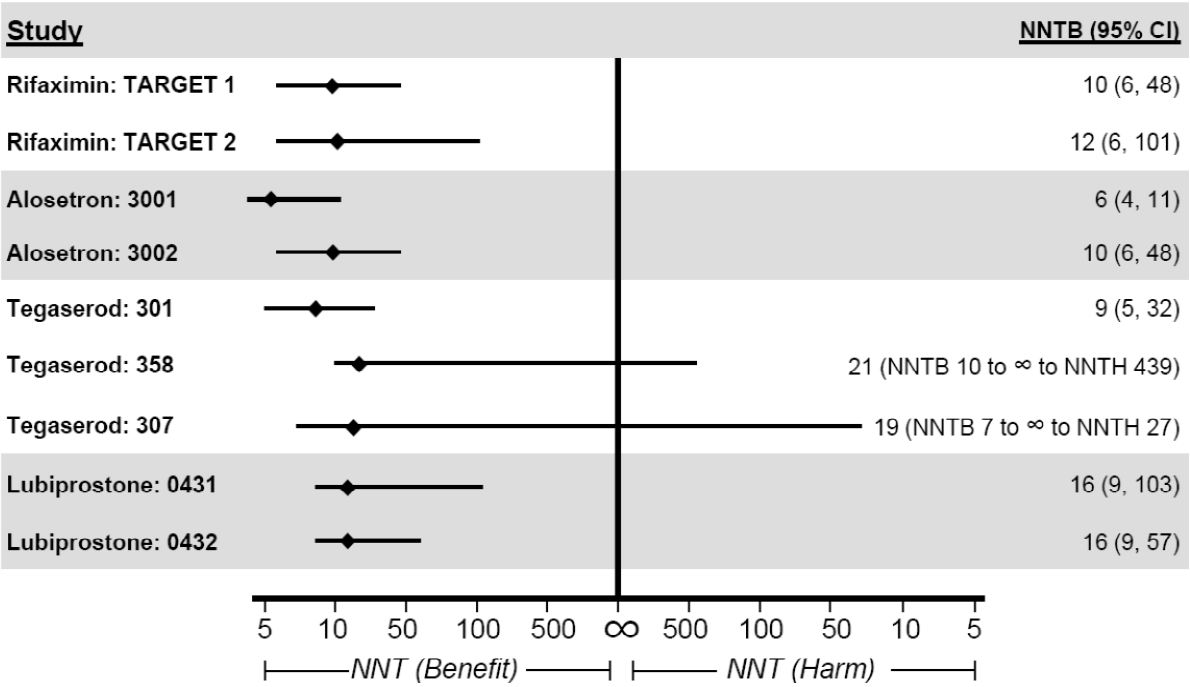
* Represents $p < 0.05$ by linear regression model comparing the LS mean change from baseline between treatment groups adjusting for analysis center, baseline, and baseline by treatment interaction.

6.6. Clinical Utility of Rifaximin

The clinical relevance of the treatment effect observed in the TARGET studies is underscored by relative comparisons to alosetron (Lotronex), tegaserod (Zelnorm), and lubiprostone (Amitiza). These drugs were previously approved by the FDA based on weekly responder results for abdominal pain and discomfort symptoms over a 12-week treatment period. Subjects received study drug or placebo daily for the complete 12-week treatment period in these studies. By contrast, rifaximin subjects received treatment for 2 weeks, and were followed for a 10-week post-treatment phase. The alosetron,[166] tegaserod,[,167] and lubiprostone[168] treatment effects were diminished immediately after therapy was withdrawn.

A comparison for the number-needed-to treat (NNT) is shown in Figure 23 for primary efficacy endpoint results for rifaximin, alosetron, tegaserod, and lubiprostone. The NNT is the estimated number of subjects who need to be treated with active treatment rather than placebo for 1 additional subject to benefit. The NNT for rifaximin was similar to the NNT for each of the other drugs. The confidence intervals for the NNT overlap, demonstrating comparable efficacy among rifaximin and the previously approved therapies for the treatment of IBS. Thus, the treatment effect observed for the primary endpoint at the primary time point (PEP) is clinically meaningful.

Figure 23 Rifaximin, Alosetron, Tegaserod, and Lubiprostone Number-Needed-to-Treat



Sources: Target 1 and Target 2 study data. Alosetron (Lotronex) data were from the Summary Basis of Approval (SBA) for NDA 21-107, tegaserod (Zelnorm) data were from the SBA for NDA 21-200, and lubiprostone (Amitiza) data were from the SBA for NDA 21-908 S005.

6.7. Phase 2b Study RFIB2001

Efficacy outcomes from the phase 3 TARGET studies confirmed findings demonstrated in phase 2b and in the published literature. Results of RFIB2001 demonstrated efficacy for rifaximin in the treatment of IBS subjects with diarrhea and were used to help guide the design of the TARGET studies. As discussed in Section 5.2, the RFIB2001 study evaluated the efficacy of rifaximin 550 mg BID versus placebo, and evaluated the relative efficacy and safety of 4 rifaximin dosing regimens (3 rifaximin doses) in subjects with IBS. Most (> 85%) subjects in the study had IBS-D.

6.7.1. Co-Primary Endpoints (RFIB2001)

Co-primary efficacy endpoints were evaluated in RFIB2001: adequate relief of global IBS symptoms and adequate relief of IBS bloating at the end of the 4-week treatment phase (Day 1 to 28; rifaximin subjects received rifaximin for 2 weeks followed by 2 weeks of placebo). These endpoints were assessed using a weekly SGA question, similar to those used in the TARGET studies. Adequate relief was defined as “yes” responses to the weekly question for at least 2 of the final 3 weeks of the 4-week Treatment Phase.

The primary analysis compared the rifaximin 550 mg BID 2 week group (N=191) versus the placebo group (N=197). In the ITT population, 52% of subjects in the rifaximin 550 mg BID 2 week group experienced adequate relief of IBS symptoms versus 44% of subjects in the placebo group (p = 0.0314; Table 14). Similarly, 46% of subjects in the rifaximin group experienced adequate relief of IBS bloating compared with 40% of subjects in the placebo group (p = 0.0402).

Table 14 RFIB2001: Adequate Relief of Global IBS Symptoms and IBS-Related Bloating at the End of the Treatment Phase (Primary Comparison, ITT Population)

Efficacy Variable	RFX 550 2w N = 191 n (%)	Placebo N = 197 n (%)	p-value
Adequate relief of global IBS symptoms			
Success	100 (52)	87 (44)	0.0314
Failure	91 (48)	110 (56)	
Adequate relief of bloating			
Success	88 (46)	78 (40)	0.0402
Failure	103 (54)	119 (60)	

Source: RFIB2001 CSR; Abbreviations: PBO = placebo; RFX = rifaximin; w = week(s); IBS = irritable bowel syndrome.

In an analysis of number of weeks of response during the treatment period in RFIB2001 (Weeks 1-4), the proportion of subjects who achieved 3 or 4 weeks of adequate relief during the 4-week treatment phase was significantly greater in the rifaximin 550 mg BID group than in the placebo group for both global IBS symptoms (40% vs. 32%) and IBS bloating (35% vs. 29%). The rifaximin 550 mg BID 2 week group had significantly higher odds of having a greater number of weeks of relief than the placebo group for both global IBS symptoms ($p = 0.0114$) and IBS bloating ($p = 0.0122$).

6.7.2. Long Term Rifaximin Treatment Effect in RFIB2001

The RFIB2001 study also assessed the duration of adequate relief for clinical responders in the study over 12 weeks of treatment-free follow-up. At Week 16, the percentage of continuing subjects with sustained adequate relief of IBS symptoms was 62% in the rifaximin group versus 49% in the placebo group (odds ratio = 3.674, $p = 0.0186$); and the percentage of continuing subjects with adequate relief of IBS bloating was 59% in the rifaximin group versus 51% in the placebo group (odds ratio = 3.700, $p = 0.0212$). Statistically significant ($p < 0.05$), between-group differences were also observed in favor of rifaximin 550 mg BID versus placebo for both endpoints at Weeks 10, 11, 13, 14, and 15. As with the TARGET studies, these results demonstrate a sustained rifaximin treatment effect with a short, 2-week course of therapy.

6.7.2.1. Other Efficacy Findings in RFIB2001

No statistically significant differences were observed between the rifaximin 550 mg BID 2 week and rifaximin 550 mg BID 4 week groups during efficacy analyses in the study. This suggested no added therapeutic benefit with treatment extending beyond 2 weeks. Exploratory analyses of efficacy data also showed a pronounced rifaximin treatment effect when subjects with extremely severe bloating and abdominal pain at baseline were excluded from the analyses. This trend indicated that patients with extremely severe symptoms do not respond as well to rifaximin treatment. In some cases, patients with extreme watery diarrhea and abdominal pain, and other excessively severe symptoms may not have IBS, but may be patients complicated with other confounding conditions.

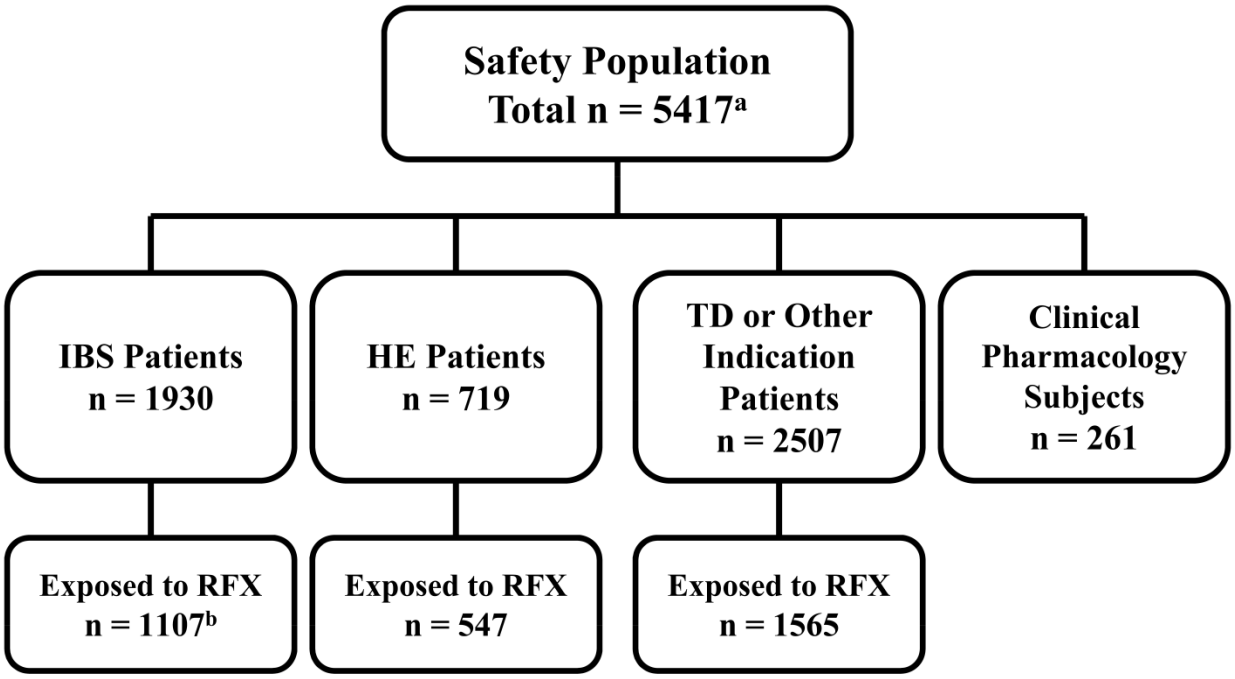
There were no statistically significant differences observed between adjacent rifaximin dose groups in the study in the pre-specified analyses. However, secondary analyses of daily IBS symptoms showed superiority in improvement in bloating, abdominal pain, and sense of urgency in the 1100 mg BID group versus placebo, suggesting that doses higher than 550 mg BID were effective.

7. Clinical Safety

The safety of rifaximin has been established through experience in multiple clinical studies in IBS and other indications with 5417 subjects (Figure 24), as well as extensive worldwide post-marketing exposure (20+ years). Salix-sponsored rifaximin studies have included IBS subjects (N = 1107), HE subjects (N = 547), TD subjects (N = 593), and healthy volunteers in pharmacology trials (N=261).

The primary safety data for the non-C IBS indication consists of 1107 subjects who were randomized to receive rifaximin, including 624 who received the proposed dosing regimen of 550 mg TID for 14 days.

Figure 24 Safety Population of Subjects in Rifaximin Clinical Studies



Abbreviations: RFX = rifaximin; IBS=irritable bowel syndrome; HE = hepatic encephalopathy; and TD=travelers' diarrhea.
a Rifaximin all doses tested or placebo/control as of October 01, 2011.
b Actual number who received at least 1 dose of rifaximin: 1103.

7.1. Summary of Supportive Safety Data

The safety profile of rifaximin for the non-C IBS indication has been well established by the nonclinical and clinical pharmacology, pharmacokinetics, and toxicology data; clinical data from > 5000 subjects enrolled in clinical studies across a range of indications; and post-marketing surveillance from countries worldwide, including the US. In vitro and in vivo data from pharmacology, toxicology, drug interaction, and pharmacokinetics studies have not indicated any safety concerns. Data from other clinical studies conducted in indications such as HE, TD, and TD prophylaxis support the tolerability and safety of rifaximin. There has not been a market withdrawal of rifaximin for safety reasons in any of the countries in which it is available.

7.2. Evaluation of Safety Data in Patients with Non-C IBS

Rifaximin is currently proposed for the treatment of non-C IBS and IBS-related bloating. In accord with the population at risk, the safety review contained in this document focuses on safety events of primary concern to this patient population. The primary safety analyses presented therefore are for the IBS population, including the phase 3 studies (TARGET 1 and TARGET 2), and the phase 2b study RFIB2001.

For long-term safety, data is summarized from the rifaximin HE program. Rifaximin 550 mg tablets BID were approved for prevention of HE recurrence as chronic, daily therapy in March of 2010. There are important differences between the HE and IBS populations that were acknowledged at the time of the meetings, namely that the HE population is a more severely ill and typically older population, and HE patients, due to their liver impairment, have a 10- to 20-fold increase in exposure to rifaximin.

7.3. Overall Extent of Exposure

In the primary Safety population (TARGET 1, TARGET 2, and RFIB2001), mean exposure to study drug was 20 days and 18 days for all rifaximin- and placebo-treated subjects, respectively. Mean compliance percentages were high for all treatment groups (> 94%).

The phase 3 safety population (TARGET 1 and TARGET 2) was comprised of 624 subjects who received rifaximin 550 mg TID (1650 mg/day) and 634 subjects who received matching placebo. In these studies, 95% of subjects in each treatment group took rifaximin for at least 14 days. For the dose groups included in the phase 2b study (RFIB2001), the mean duration of exposure was ~ 28 days in each rifaximin group. For the 2-week rifaximin regimens, subjects received active drug for 2 weeks and then placebo for 2 weeks, for a total duration of 4 weeks. Subjects in the placebo group received placebo for 4 weeks.

7.4. Subject Disposition

Subject disposition is summarized for the TARGET studies in Section 5.1.3 and for the RFIB2001 study in Section 5.2.2. In total, 1260 subjects were randomized into the TARGET studies, 625 in the rifaximin 550 mg TID treatment group and 635 in the placebo group. In each treatment group, the vast majority of participating subjects completed the 2-week treatment phase (> 97%) and the 10-week follow-up phase (> 93%). There were no notable differences between treatment groups for each of the primary reasons for early discontinuation.

In RFIB2001 a total of 680 subjects were randomized and entered the treatment phase of the study. A total of 197 subjects were randomized to placebo for 4 weeks and 483 subjects were randomized to 1 of 4 rifaximin treatment regimens: 275 mg BID (N=95), 550 mg BID for 2 weeks (N=191), 550 mg BID for 4 weeks (N=98), or 1100 mg BID (N=99). Most subjects (> 88%) completed the treatment phase. A total of 249 subjects responded to treatment in RFIB2001 and entered the 12-week follow-up phase of the study; approximately half (51%) of these completed the follow-up phase. There were no notable differences between treatment groups for each of the primary reasons for early discontinuation.

Demographics and baseline characteristics for subjects in TARGET 1, TARGET 2, and RFIB2001 are described in Sections 5.1.4 and 5.2.2.

7.5. Summary of Adverse Events

During the 12-week TARGET studies and the 16-week RFIB2001 study, 53% of all rifaximin subjects and 53% of placebo subjects experienced at least 1 AE (Table 15). Most AEs in these studies were mild or moderate in intensity, and there were few SAEs or AEs resulting in study discontinuation. There were no remarkable differences among the rifaximin dose groups and the placebo group in the incidence of AEs, drug-related AEs, severe AEs, SAEs, and AEs resulting in study discontinuation.

Table 15 Overall Summary of Adverse Event Incidence (TARGET 1, TARGET 2, and RFIB2001)

	Rifaximin						
Category	**275 mg BID 2 Weeks N = 95 n (%)**	**550 mg BID 2 Weeks N = 190 n (%)**	**550 mg BID 4 Weeks N = 96 n (%)**	**550 mg TID 2 Weeks N = 624 n (%)**	**1100 mg BID 2 Weeks N = 98 n (%)**	**All Rifaximin N = 1103 n (%)**	**Placebo N = 829 n (%)**
Any AEs	50 (53)	95 (50)	42 (44)	340 (55)	52 (53)	579 (53)	436 (53)
AEs by Intensity							
Severe	5 (5)	14 (7)	3 (3)	36 (6)	5 (5)	63 (6)	53 (6)
Moderate	21 (22)	35 (18)	15 (16)	161 (26)	14 (14)	246 (22)	214 (26)
Mild	24 (25)	46 (24)	24 (25)	142 (23)	32 (33)	268 (24)	169 (20)
AEs Related to Study Drug	10 (11)	25 (13)	9 (9)	75 (12)	15 (15)	134 (12)	89 (11)
SAEs	1 (1)	2 (1)	0	10 (2)	3 (3)	16 (2)	18 (2)
AEs Resulting in Study Discontinuation	3 (3)	7 (4)	2 (2)	8 (1)	2 (2)	22 (2)	14 (2)
Deaths	0	0	0	0	0	0	0

Source: TARGET 1, TARGET 2, and RFIB2001 Study Data
Abbreviations: BID = twice daily; IBS = irritable bowel syndrome; ISS = Integrated Summary of Safety; AE = adverse event; SAE = serious adverse event; and TID = 3 times daily.

7.5.1. Common AEs in TARGET 1, TARGET 2, and RFIB2001

Table 16 presents a summary of AEs that occurred in at least 2% of rifaximin- or placebo-treated subjects in the IBS treatment studies. The incidences of AEs by system organ class and by preferred term were generally comparable between rifaximin- and placebo-treated subjects. The most common AEs experienced during the overall evaluation period (treatment plus follow up) by rifaximin subjects were headache (rifaximin 5%, placebo 6%), nausea (4%, 4%), diarrhea (3%, 3%), and urinary tract infection (3%, 2%).

Table 16 Adverse Events in at Least 2% of Rifaximin- or Placebo-Treated Subjects (TARGET 1, TARGET 2, and RFIB2001)

System Organ Class Preferred Term	Rifaximin					All Rifaximin N = 1103 n (%)	Placebo N = 819 n (%)
	275 mg BID 2 Weeks N = 95 n (%)	550 mg BID 2 Weeks N = 190 n (%)	550 mg BID 4 Weeks N = 96 n (%)	550 mg TID 2 Weeks N = 624 n (%)	1100 mg BID 2 Weeks N = 98 n (%)		
Subjects with any AEs	50 (53)	95 (50)	42 (44)	340 (55)	52 (53)	579 (53)	436 (53)
Gastrointestinal disorders							
Nausea	7 (7)	7 (4)	3 (3)	27 (4)	4 (4)	48 (4)	31 (4)
Abdominal pain	1 (1)	4 (2)	2 (2)	29 (5)	5 (5)	41 (4)	39 (5)
Diarrhea	2 (2)	2 (1)	4 (4)	27 (4)	2 (2)	37 (3)	26 (3)
Vomiting	2 (2)	1 (1)	3 (3)	15 (2)	1 (1)	22 (2)	12 (1)
Infections and infestations							
Upper resp tract infection	5 (5)	7 (4)	1 (1)	35 (6)	2 (2)	50 (5)	47 (6)
Urinary tract infection	5 (5)	10 (5)	4 (4)	12 (2)	6 (6)	37 (3)	18 (2)
Nasopharyngitis	0	4 (2)	1 (1)	19 (3)	2 (2)	26 (2)	39 (5)
Sinusitis	1 (1)	4 (2)	2 (2)	17 (3)	0	24 (2)	23 (3)
Musculoskeletal and connective tissue disorders							
Back pain	2 (2)	6 (3)	3 (3)	10 (2)	1 (1)	22 (2)	19 (2)
Nervous system disorders							
Headache	4 (4)	7 (4)	7 (7)	38 (6)	3 (3)	59 (5)	51 (6)

Source: TARGET 1, TARGET 2, and RFIB2001 Study Data
Abbreviations: BID = twice daily; IBS = irritable bowel syndrome; ISS = Integrated Summary of Safety; TEAE = treatment-emergent adverse event; TID = 3 times daily; and Upper resp tract infection = upper respiratory tract infection.

7.5.1.1. Common Adverse Events in Phase 3 (TARGET 1 & TARGET 2)

The safety of rifaximin tablets in the proposed 550 mg TID regimen was evaluated in 624 non-C IBS rifaximin subjects versus 634 placebo subjects in the TARGET trials. During the 2-week treatment phase of these studies, approximately 30% of subjects in each treatment group experienced an AE (rifaximin: 29%, placebo: 30%). The most common AEs in the treatment phase in the rifaximin group were headache (rifaximin 4%, placebo 4%), abdominal pain (3%, 3%), and nausea (3%, 2%) (Table 17).

During the overall 12-week evaluation period, approximately half of the subjects in each treatment group experienced an AE (rifaximin 55%, placebo 53%). The most common AEs were headache (rifaximin 6%, placebo 7%), upper respiratory tract infection (6%, 6%), and abdominal pain (5%, 6%); all of these occurred in a slightly larger proportion of the placebo group compared to the rifaximin 550 mg TID group (Table 17).

Table 17 Adverse Events Occurring in at Least 2% of Rifaximin Subjects in Phase 3 (TARGET 1 & TARGET 2 Combined Data)

Preferred Term	Rifaximin 550 mg TID N = 624 n (%)	Placebo N = 634 n (%)
2-Week Treatment Phase		
Headache	25 (4)	28 (4)
Abdominal pain	17 (3)	17 (3)
Nausea	16 (3)	12 (2)
Nasopharyngitis	4 (1)	18 (3)
Upper respiratory tract infection	4 (1)	14 (2)
Overall 12-Week Evaluation Phase		
Headache	38 (6)	42 (7)
Upper respiratory tract infection	35 (6)	39 (6)
Abdominal pain	29 (5)	35 (6)
Nausea	27 (4)	24 (4)
Diarrhea	27 (4)	22 (4)
Nasopharyngitis	19 (3)	34 (5)
Sinusitis	17 (3)	16 (3)
Vomiting	15 (2)	9 (1)
Bronchitis	13 (2)	17 (3)
Cough	13 (2)	9 (1)

Source: TARGET 1 & 2 Safety Data
Abbreviations: TID = 3 times daily

7.5.2. AEs by Relationship and Intensity in TARGET 1 & TARGET 2, and RFIB2001

The most frequently occurring drug-related AEs in the non-C IBS studies were GI disorders and nervous system disorders. The following drug-related AEs were experienced during the treatment phase by ≥ 1% of subjects in either treatment group: nausea (rifaximin 2%, placebo 1%), headache and flatulence (1% each), and abdominal pain (1%, 2%). The incidence of drug-related AEs was similar between the treatment phase (rifaximin 11%, placebo 9%) and the overall evaluation phase (treatment plus follow-up: 12%, 11%).

By intensity, severe AEs were reported for 6% of subjects in both the rifaximin and placebo groups in the non-C IBS studies. No severe AEs occurred in ≥ 1% of rifaximin or placebo subjects during treatment and follow-up. There were no notable between-group differences in the profile and incidence of severe AEs.

7.6. Deaths, SAEs, and AEs Leading to Discontinuation (TARGET 1 & 2, and RFIB2001)

7.6.1. Deaths

No subjects died in any of the studies of rifaximin for the treatment of non-C IBS.

7.6.2. Serious Adverse Events

SAEs were experienced in 1.5% and 2.2% of rifaximin- and placebo-treated subjects, respectively. There were no reports of SAEs involving constipation, ischemic colitis, or death.

Serious AEs reported for the rifaximin group were as follows (each in 1 subject unless otherwise noted): alcohol withdrawal syndrome; appendicitis; atrial fibrillation; breast cancer;

costochondritis; Crohn's disease; hypertension; intervertebral disc displacement; meningitis; non-cardiac chest pain; road traffic accident; chest pain (2 subjects); bronchitis and chronic obstructive pulmonary disease (both events in 1 subject); diarrhea, nausea, and vomiting (all 3 events in 1 subject); and dehydration, hypoxia, respiratory acidosis, hypotension, confusional state, and disorientation (all 6 events in 1 subject).

No preferred term for an SAE occurred in more than 1 rifaximin-treated subject, except chest pain which was reported in 2 subjects, and 1 of these was noted to be non-cardiac in nature.

7.6.3. Adverse Events Resulting in Study Discontinuation

The incidence of discontinuations due to AEs in the IBS studies was low and similar between treatment groups (rifaximin 2.0%, placebo 1.7%). Adverse events that led to discontinuation from the studies for more than 1 rifaximin-treated subject were worsening IBS (rifaximin 0.4%, placebo 0) and constipation (0.2%, 0.1%). Worsening diarrhea led to discontinuation from the studies for 0.5% of placebo subjects; no rifaximin subjects discontinued as a result of worsening diarrhea.

7.7. Adverse Events of Special Interest in IBS Population

An analysis of AEs of special interest was performed on the basis of known and potential side effects of antibiotics as a drug class, with specific focus on AEs that are of interest to patients with IBS. These special interest AEs included GI-related events, infections, hypersensitivity events, and other events of concern in the general population such as cardiac and hepatic events.

7.7.1. Evaluation of Gastrointestinal Disorders

The frequencies of GI-related AEs were balanced between treatment groups (rifaximin and placebo) during the IBS studies. The incidence of diarrhea (i.e., worsening diarrhea) was similar between treatment groups (rifaximin 3.4%, placebo 3.1%), as was the incidence of constipation (1.1%, 1.8%). No subject experienced an SAE of ischemic colitis or any other serious complications related to constipation.

7.7.2. Evaluation of Infections

The frequencies of infection-related AEs were balanced between treatment groups during the treatment phase and overall evaluation period (treatment plus follow-up). The most frequently occurring AEs (≥ 1% of subjects in either group) involving infections during the 2-week treatment phase were nasopharyngitis (rifaximin 0.7%, placebo 2.4%), upper respiratory tract infection (1.3%, 2.3%), and urinary tract infection (1.7%, 0.8%).

During the follow-up phase, AEs associated with infections were recorded for similar proportions of subjects in the all rifaximin (14.9%) and placebo (15.8%) groups. The profile of infections was similar in the treatment and follow-up phases of the study. No rifaximin-specific trends with respect to infection were observed during extended treatment follow-up (10 to 12 weeks).

With regards to infections, the current product labeling for XIFAXAN provides information for physicians (see Appendix 1). As is the case with all antibiotics, physicians are informed about the risk of *C. difficile* infection. One case of *C. difficile* infection was recorded in the IBS development program, but onset was prior to first rifaximin dose. A stool sample provided prior to the subject receiving her first dose of rifaximin (550 mg BID in RFIB2001) cultured positive

for *C. difficile*; the investigator considered the infection not to be related to the study drug. There has been no indication of the development of clinically significant bacterial resistance.

Salix believes the current label adequately and responsibly informs physicians about the possibility of infections with rifaximin. The current XIFAXAN label has the following under 'warning and precautions:'

'5.1 Travelers' Diarrhea Not Caused by *Escherichia coli*'

'XIFAXAN were not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than Escherichia coli.

Discontinue XIFAXAN if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

XIFAXAN is not effective in cases of travelers' diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. XIFAXAN should not be used in patients where *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.'

'5.2 *Clostridium difficile*-Associated Diarrhea'

'*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.'

7.8. Clinical Laboratory Data

There were no rifaximin-specific trends in clinical laboratory test results in the IBS studies. The incidences of subjects with postbaseline elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, gamma glutamyltransferase, and ALT > 3 × upper limit of normal (ULN) concurrent with total bilirubin > 2 × ULN were investigated. The incidence of post-baseline elevations was low (0 to ≤ 0.5%) in both the rifaximin and placebo groups and no subjects had concurrent elevations of ALT > 3 × ULN with total bilirubin > 2 × ULN. There were no imbalances between placebo and rifaximin treatment groups for other clinical laboratory observations related to hepatic function.

7.9. Adverse Events in Special Populations

The influence of intrinsic factors on the AE profile of rifaximin, including AEs, SAEs, and AEs resulting in discontinuation from the study was examined using gender, age (< 65, ≥ 65), and race

(white, nonwhite) subgroup analyses. Based on results of these analyses, no dose modifications are recommended with respect to any of these factors.

7.10. Long-Term Safety Data

Long-term safety data are available for 392 unique subjects who received rifaximin at a dose of 550 mg BID (1100 mg/day) for up to 1427 days (mean: 476 days) for the reduction in risk of HE recurrence in Salix studies RFHE3001 (6-month, double-blind, placebo-controlled) and RFHE3002 (3+ years, open-label). These studies supported the approval of rifaximin 550 mg BID for the prevention of HE recurrence as chronic, daily therapy.

At the EOP2 meeting in 2007, the FDA recommended supplementing the IBS safety database with long-term exposure to rifaximin because there is a potential for repeat courses of treatment as a result of the chronic nature of IBS. During discussions at the EOP2 and pre-NDA meetings, the FDA agreed that the safety of rifaximin during long-term exposure could be established using data from the HE program. There are important differences between the HE population and the IBS population that were acknowledged at the time of the meetings:

1. The HE population is a more severely ill and typically older population than the IBS population.
2. HE patients, due to their hepatic impairment, have a 10- to 20-fold increase in exposure to rifaximin, compared with exposures seen in IBS patients.

Table 18 Overview of Rifaximin Studies for Reduction in Risk of Overt HE Recurrence

Category	RFHE3001	RFHE3002
Subject Population	Subjects in remission from HE ≥ 18 years of age	Rollover RFHE3001 subjects or new subjects in demonstrated remission from HE; ≥ 18 years of age
Treatment Groups	Rifaximin 550 mg BID; placebo BID	Rifaximin 550 mg BID
Treatment Duration	6 months	> 3 years
Countries	US, Canada, Russia	US, Canada, Russia
Number of Subjects	299 total subjects (rifaximin: 140; placebo: 159) from 70 centers	322 total subjects (all rifaximin) from 60 centers, open label

Source: RFHE3001 & RFHE3002 study reports
Abbreviations: BID = twice daily; HE = hepatic encephalopathy; and US = United States.

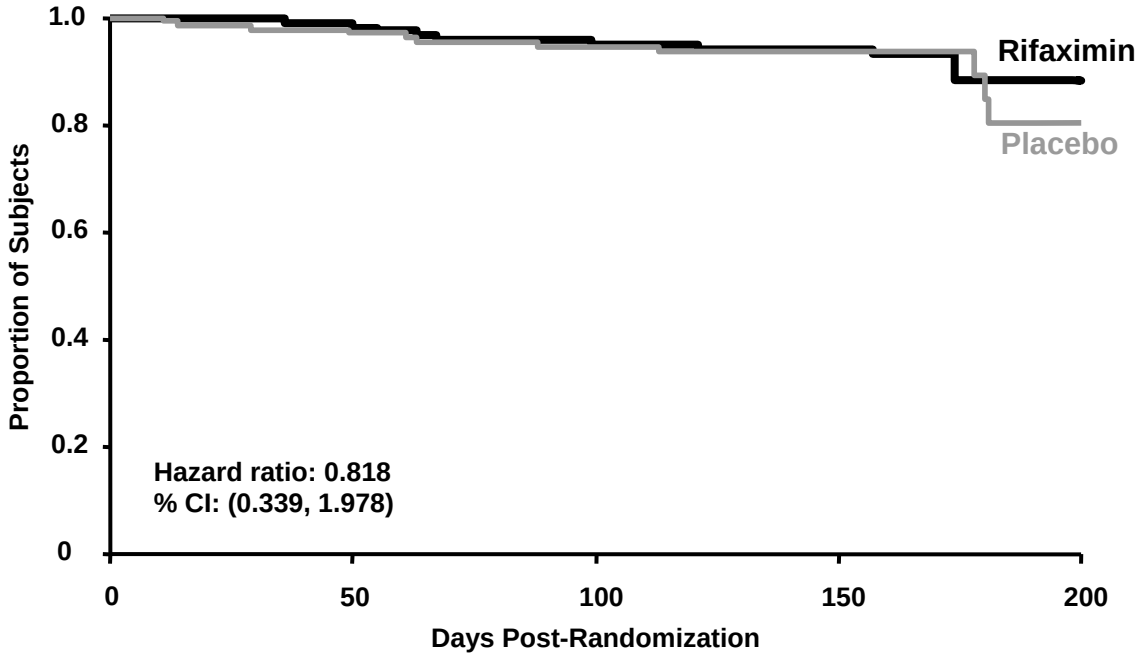
7.10.1. Summary of Long-Term Safety in Rifaximin HE Program

Long-term daily use of rifaximin 550 mg BID for HE supports the overall safety profile and establishes the safety of chronic use of rifaximin. Key safety findings for these studies are described below.

- The overall profile of AEs in the HE studies was consistent with the population under study, i.e., subjects with advanced liver disease and history of overt HE. The most frequent events are those typically expected in patients with advanced liver disease.
- In RFHE3001, AEs occurred in 80% of subjects in each group. SAEs (rifaximin 36%, placebo 40%) and AEs leading to discontinuation (21%, 28%) were experienced by a higher percentage of placebo subjects than rifaximin subjects.

- SAEs which occurred in at least 3% of rifaximin-treated subjects during the combined RFHE3001 and RFHE3002 studies were HE episode (24%), renal failure acute (8%), hepatic failure (6%), anemia (6%), hepatic cirrhosis (4%), ascites (5%), cellulitis (4%), pneumonia (4%), and GI hemorrhage (3%). These SAEs were consistent with expected events in this patient population and comparable to the SAE profile observed with placebo.
- AEs related to areas of primary concern in this patient population including blood and lymphatics, GI disorders, hepatobiliary disorders, and infections were comparable and consistent with the known incidence in the population and patient medical histories.
- Rifaximin treatment did not adversely affect mortality in patients with end-stage liver disease. There was no difference in the survival probability observed in the Kaplan-Meier analysis comparing mortality in subjects in RFHE3001 (Figure 25). The long-term RFHE3002 study had a lower death rate than in RFHE3001, and most deaths in each study appeared to be associated with the progression of underlying liver disease. The observed death rate and causes of death in the rifaximin HE studies were reflective of what is described in the literature for patients with advanced liver disease.[169,170]

Figure 25 Survival Analysis for Subjects Who Died Within 30 Days of Last Dose (RFHE3001)



Source: RFHE3001 and RFHE3002 Safety Data. Note: Hazard ratio estimate (hazard of death for rifaximin compared to placebo) was obtained from Cox proportional hazards model with effect for treatment, stratified by analysis region.

- There was no indication of clinically significant bacterial resistance during long-term, daily use (> 3 years) in the HE program.
- The incidences of AEs related to infections were ~ 30% in the rifaximin and placebo groups in RFHE3001. This was consistent with the expected frequency of infections (30-60%) in subjects with advanced liver disease[171] and with subject baseline medical histories of infection (~ 60% had a past history of infection). When normalized for exposure, event

rates for infections during long-term treatment in RFHE3002 were lower than that observed in RFHE3001.

- A total of 392 patients were treated for 510 person exposure years (PEY) with rifaximin in the combined exposure of RFHE3001 and RFHE3002. The rate of infections over this prolonged exposure period was 71.8 per 100 PEY (95% CI: 65.2, 78.4), lower than rates observed in the 6-month RFHE3001 study. In RFHE3001, the infection rate for rifaximin was 111.2 per 100 PEY (95% CI: 85.1, 139.7), and for placebo was 132.1 per 100 PEY (95% CI: 101.8, 165.6) over 50 and 46 person exposure years respectively. These data indicate no increased risk of developing infection with longer exposures to rifaximin.
- The total number of GI-derived infections was also comparable between the rifaximin and placebo groups in RFHE3001, and similar or lower rates were observed in RFHE3002. A total of 5 subjects had a report of a *C. difficile* infection over the 510 patient years of exposure in RFHE3001/3002. At baseline, 6 subjects in RFHE3001/3002 had a medical history of *C. difficile* infection. *Thus, the* incidence in the studies appears equivalent to that seen in the medical history (~1% in both) and the expected rate in subjects with a*dvanced liv*er disease.[172] The *C. difficile* infection resolved for each of the 5 subjects following either vancomycin or metronidazole therapy. Three of the 5 subjects remained on rifaximin or receiv*ed off-study* XIFAXAN following resolution. All 5 subjects had recent clinical histories that included several risk factors for infection, including hepatic cirrhosis, advanced age, hepatitis C, numerous hospitalizations with multiple courses of antibiotics other than rifaximin, and concurrent use of proton pump inhibitors. Two of the 5 subjects were diagnosed with *C. difficile* infections > 20 days after last dose of rifaximin. Both of these events followed hospitalization and the use of systemic antibiotics.
- In a recent retrospective study examining the incidence of *C. difficile* infection in cirrhotic patients, patients taking rifaximin treatment had a significantly lower incidence of *C. difficile* associated diarrhea than those taking lactulose ($p < 0.007$).[79] In results presented at AASLD 2011 from a second retrospective study, rates of antibiotic-resistant infection in hospitalized cirrhotic patients were studied. Compared with an odds ratio of 1 for patients with no antibiotic exposure in the prior 30 days, patients receiving a systemic antibiotic had an odds ratio of 4.8 (95% CI: 1.5 – 15.4) compared with patients receiving a non-systemic antibiotic (primarily rifaximin), with an odds ratio of 0.48 (95% CI: 0.12 – 2.01). The data indicate that recent exposure to systemic, but *not* non-systemic, antibiotics was the primary predictor of the development of antibiotic-resistant infection.[80]
- Clinical laboratory evaluations revealed no notable imbalances between rifaximin and placebo in post-baseline elevations in liver function tests (e.g., ALT, AST, bilirubin) or in AEs and SAEs that reflect impaired hepatic function. In analyses of renal function laboratory parameters and observed AEs for renal and urinary disorders, rifaximin did not appear to have an impact on renal function in these studies.

7.11. Evaluation of Bacterial Resistance

Salix is committed to ongoing close monitoring of rifaximin for patterns of bacterial resistance. To date, there has been no indication of clinically significant bacterial resistance occurring in the IBS population, or during long-term, daily use in cirrhotic patients in the approved HE population

(see Sections 7.7.2 and 7.10.1). Rifaximin resistance has already been extensively studied in multiple in vivo and in vitro studies, and resulting data indicate a low risk of significant antibiotic resistance or cross-resistance (see Section 4.2).

Multiple factors differentiate rifaximin from systemic, broad-spectrum antibiotics. Resistance to rifaximin is not plasmid-mediated but instead requires a stable mutation in host cell DNA; therefore, dissemination of resistance and cross-resistance to other antibiotics by plasmid-based mechanisms is eliminated. Rifaximin also does not promote the emergence of bacterial cross-resistance to rifampin, as has been demonstrated in studies examining *C. difficile* in vivo and *C. difficile, E. coli*, and *M. tuberculosis* in vitro.[173,174,175,176] Therefore, use of rifaximin to treat the intestinal dysbiosis associated with IBS is not expected to alter the utility of systemic or other enteric antibiotics to treat overt infections at those sites.

Salix will monitor the effects of rifaximin on gut flora, including resistance, in upcoming phase 4 HE studies RFHE4043 and RFHE4044, as part of post-marketing commitments for the approved HE indication.

7.12. Supportive Safety Findings

The nonclinical toxicology program for rifaximin included single-dose toxicology studies in mice and rats, repeat dose oral toxicology studies for up to 26 weeks in rats and up to 39 weeks in dogs; in vivo safety pharmacology, reproductive toxicity, genotoxicity, and carcinogenicity studies; and in vitro inhibition studies.

Single dose toxicology, safety pharmacology, reproductive toxicity, genotoxicity, and carcinogenicity studies resulted in no toxicities attributable to rifaximin exposure. In repeat dose toxicology studies, findings in rats at study durations up to 26 weeks were limited to decreases in weight gain and peripheral lymphocyte count. In dogs, at doses up to 3000 mg/kg/day (for 7 days) and 1000 mg/kg/day (for 39 weeks), orange feces/fur (attributed to the orange color of rifaximin) and nonspecific stress-induced thymic atrophy were reported; no consistent pathologic or histopathologic changes attributable to rifaximin were observed. Specific to the patient population under study in the current application, no histopathology suggesting hepatic effects of rifaximin was reported in rodent or nonrodent species.

In vitro, the effects of rifaximin on the human bile salt export pump (BSEP), the primary transporter regulating ATP-dependent bile salt translocation from the liver to the bile, was quantitated; it was a weak inhibitor with an IC_{50} of 83 μM. This weak inhibition indicates a minimal risk of clinically significant BSEP inhibition.

Rifaximin concentrations up to 300 μM failed to achieve 50% inhibition of the hERG potassium current in vitro, leading to an estimated IC_{50} of >100 μM.[177] This value is more than 3000 times greater than the highest C_{max} observed in any rifaximin-treated subject to date, a safety margin that greatly exceeds the 30-fold separation that is commonly associated with minimization of risk of clinical QT interval prolongation.

7.13. Summary of Important Foreign Actions

No license application rejections or withdrawals from the market have been reported since rifaximin was first approved for marketing. Rifaximin was first approved in 1985 in Italy and is currently approved in 36 countries for various GI or GI-related indications.

8. Proposed Rifaximin Repeat Treatment Study

Rifaximin is the first IBS treatment to demonstrate persistent efficacy following completion of a short course (2 weeks) of therapy. Repeat treatment efficacy for subjects who initially responded to rifaximin and experienced symptom recurrence was not studied in the clinical program. As a result, the FDA has requested prospective, controlled clinical evidence that rifaximin is effective with repeat treatment following recrudescence of symptoms.

8.1. Repeat Treatment Study Design Considerations

Repeat treatment (i.e., re-treatment) as a focus for study design poses several challenges for clinical researchers. There are few accepted best practices for repeat treatment studies and often there can be debate about what type of repeat treatment is optimal for patients in a given indication: repeat treatment to prevent recurrence of symptoms or repeat treatment only following recrudescence of symptoms. Other important considerations include, but are not limited to, adequately defining what constitutes patient recurrence and what constitutes continued response in the disease or disorder being studied.

Irritable bowel syndrome is well known for being a particularly "hard-to-study" GI disorder.[6] Patients with IBS present with variable symptomatology, and these symptoms are chronic, recurring, and unstable. The waxing and waning of symptoms that naturally occurs in IBS patients can make assessments of efficacy difficult, particularly long-term efficacy.[178,179,180,181,182] For example, if a drug's effect is assessed during a natural waning period of low symptom intensity or spontaneous remission, it can be very difficult to demonstrate a treatment benefit, even where one exists. For these reasons IBS clinical trials have traditionally been associated with a high placebo response, likely due to the temporal nature of IBS symptoms and the symptom variability that exists between individual patients.

The draft FDA guidance for evaluation of IBS products (March 2010) recommends that IBS trials use a randomized, parallel-group, placebo-controlled design. This is consistent with previous guidance from the Committee for Proprietary Medicinal Products and the established standards for past research in IBS.[178] The FDA also recommends that IBS clinical trials enroll patients who meet subtype-specific Rome III IBS diagnostic criteria. For primary efficacy analyses, the FDA recommends a composite abdominal pain and stool consistency endpoint for IBS with diarrhea (see Section 2.5). The proposed repeat treatment study (Section 8.3) was planned to be consistent with FDA draft guidance and to control for the challenges associated with analyzing repeat use in this indication.

8.2. Existing Data for Repeat Rifaximin Treatment in IBS

Data is currently available on the efficacy of repeat treatment with rifaximin in IBS in 4 retrospective chart review studies in the published literature (Table 19).[81,82,83,84] Findings from these studies suggest that rifaximin-treated patients who develop a recurrence of IBS symptoms are being safely and successfully retreated by their physicians. In brief, the available information about repeat treatment suggests that re-treatments with rifaximin results in:

- A high probability of success with > 75% of responders being re-treated successfully; and
- Infrequent treatment with an average time to a repeat treatment of > 6 months.

Table 19 Existing Data for Repeat Rifaximin Use in IBS

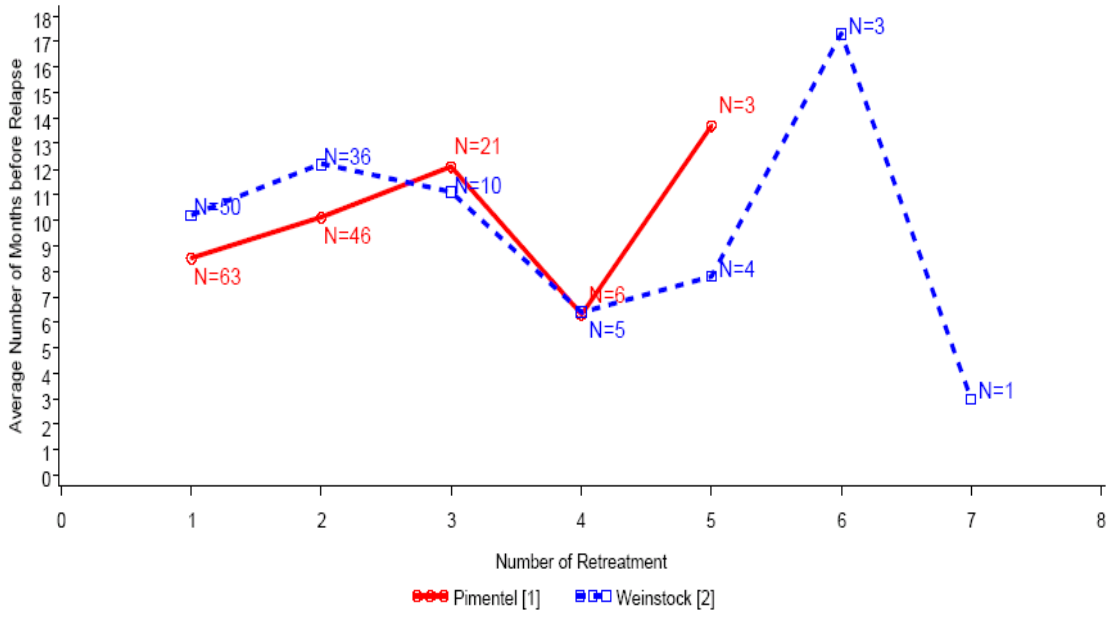
Study (Duration) Population	RFX Dose and Duration	Number of Re-treatments	Results
Pimentel, et al. (> 6 yr)[81] 169 Non-C IBS Patients (Rome III)	• 400-550 mg TID for 14 days	1 to 6 re-treatments	- Initial treatment response: 75% (111/148) - Re-treatment response (at least 1): > 75% - First: 54/65 Second 38/40: Third: 17/18 - Duration of benefit is ~4 m
Weinstock (> 6 yr)[82] 99 Non-C IBS Patients (Rome II)	• 1200-1650 mg/day for 10 days	1 to 5 re-treatments	- Initial treatment response: 75% (74/99) - 27% did not require re-treatment - 41% maintained response for mean 1.6 y - 51% only 1-2 retreatment in 2 y
Jolley (~1 yr)[83] 162 IBS Patients (Rome III; 28% IBS-D)	• 1200 mg/day for 10 days	2400 mg/day for 10 days (if no response in 2- 4 weeks)	For IBS –D patients: - Initial treatment response: 56% (25/45) - Re-treatment response (at least 1): 54% (13/24) - Complete(>90%) relief: 11% (5/45) - Complete (>90%) relief upon re-treatment: 13% (3/24)
Yang, et al (1.25 yr)[84] 84 IBS Patients (Rome I)	• 1200 mg/day for 10 days	1200 mg/day for 10 days	- Initial treatment response: 69% (58/84) - Re-treatment response (at least 1): 100% - First : 16/16 Second 4/4 - Initial response to antibiotic other than rifaximin: 38% (27/61) - Retreatment response to antibiotic other than rifaximin: 25% (2/8)

Abbreviations: IBS = irritable bowel syndrome; non-C IBS = non-constipation IBS; IBS-D = diarrhea-predominant IBS; RFX = rifaximin; and TID = 3 times daily.

These studies also indicate that patients do not appear to develop tolerance after receiving multiple courses of rifaximin (Figure 26).

Thus, findings from the literature indicate that re-treating IBS patients with rifaximin in the clinical setting provides a high probability of success as well as an infrequent need.

Figure 26 Duration of Benefit Between Re-Treatments with Rifaximin



[1] Data from Pimentel M, Morales W, Chua K , Barlow G, Weitsman S, Kim G, Amichai MM, Pokkunuri V, Rook E, Mathur R, Marsh Z. Effects of Rifaximin Treatment and Retreatment in Nonconstipated IBS Subjects In press, Dig Dis Sci. 2011
[2] Data from Weinstock LB. Long-term Outcome of Rifaximin Therapy in Non-constipation Irritable Bowel Syndrome Patients. Submitted to Journal of Clinical Gastroenterology

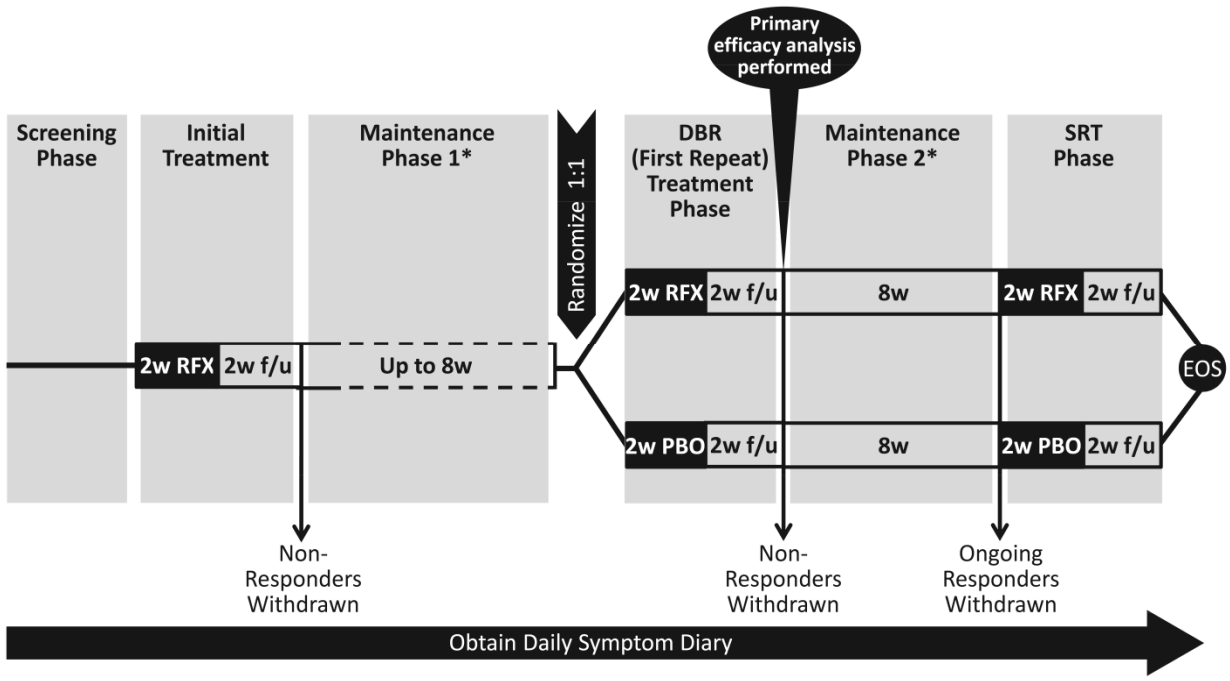
8.3. Proposed Repeat Treatment Study Design

Salix has developed a repeat treatment study proposal to address points raised by the FDA in the CRL. This proposed study will assess the benefit of repeat treatment with rifaximin in IBS patients, as well as add to the existing evidence for rifaximin's efficacy and safety in this indication. Salix has worked collaboratively with the FDA in this process and actively sought feedback to ensure that appropriate design elements are included. The proposed study is a multi-center, randomized, double-blind, placebo-controlled trial in adult subjects with non-C IBS confirmed using Rome III diagnostic criteria. The primary study objective will be to evaluate the efficacy of repeat treatment with rifaximin 550 mg TID in subjects who responded to initial treatment with rifaximin. The study design is illustrated below in Figure 27.

Participating subjects will use an IVRS to record their daily IBS symptoms for efficacy assessments. The primary efficacy measure is treatment success for abdominal pain AND stool consistency, consistent with the IBS-D endpoint from the draft FDA guidance. **Response** in the study is defined as subjects who experience treatment success for IBS-related abdominal pain AND stool consistency for at least 2 out of 4 weeks during a 4-week assessment period. A subject will be considered to have met **Recurrence** criteria when treatment success of abdominal pain AND stool consistency is absent for at least 3 weeks during a 4-week assessment period (an alternate possibility for the definition of recurrence will be the absence of treatment success of abdominal pain AND stool consistency for any 3 consecutive weeks).

The total study duration is approximately 30 weeks, depending on whether a colonoscopy is required. The study includes the Primary Repeat Treatment Efficacy analysis to be conducted at the end of the Double-Blind, Randomized (first repeat) Treatment Phase (i.e., Week 16 of the study) to evaluate the benefit of repeat treatment with rifaximin in the non-C IBS population. Results from this analysis will be submitted to the FDA as a primary component of Salix's complete response to the CRL. This provision was included based on discussions with the FDA and would allow for a more timely response to the CRL, with due consideration for the urgency of the unmet need in IBS. Salix would continue to collect data during the remainder of the study to further augment the understanding of repeat use of rifaximin in this patient population.

Figure 27 Proposed Repeat Treatment Study Design



Abbreviations: RFX = rifaximin; PBO = placebo; f/u = follow-up; DBR = Double-Blind, Randomized; SRT = Second Repeat Treatment; and EOS = end of study.

*During the Maintenance Phases subjects with recurrence enter the Repeat Treatment Phases:
- Maintenance Phase 1: Subjects who do not meet recurrence criteria by the end of the 8 week Maintenance Phase will be allowed to continue up to an additional 12 weeks until they experience recurrence; or until enrollment is met in DBR (Repeat Treatment) Phase.
- Maintenance Phase 2: Subjects who do not meet recurrence criteria by the end of 8 weeks will be withdrawn from the study.

The study will consist of the following phases:

- **Screening Phase (up to 30 days)** – Potential subjects will undergo screening assessments including a colonoscopy, if necessary, and complete a Diary Eligibility Period of at least 7 days. During the Diary Eligibility Period, subjects will be required to respond to daily IBS symptom related questions.

- **Initial Treatment Phase (4 weeks)** – Eligible subjects will receive a 2-week course of rifaximin 550 mg TID, with 2 weeks of treatment-free follow-up. At the end of this initial treatment and follow-up phase, subjects will be assessed for response. Subjects who are

responders will enter a treatment- free maintenance phase (i.e., Maintenance Phase 1) whereas non-responders will be withdrawn from the study.

- **Maintenance Phase 1 (up to 8 Weeks) -** This phase will be variable in duration for subjects, depending on whether or not there is a recurrence of IBS symptoms. Subjects will be continually assessed for ongoing response as well as recurrence of IBS symptoms starting after 2 weeks in Maintenance Phase 1. Subjects who meet the criteria for recurrence will enter the Double-Blind, Randomized (first repeat) Treatment) Phase. Subjects who do not meet recurrence criteria by the end of Maintenance Phase 1 will be allowed to continue up to an additional 12 weeks (20 weeks total) until they either experience recurrence; a full 24 weeks from initial treatment has elapsed without recurrence; or until enrollment is met in the Double-Blind, Randomized (first repeat) Treatment Phase.

- **Double-Blind, Randomized (first repeat) Treatment Phase (4 Weeks) and Interim Analysis –** In this phase, subjects who experienced recurrence during Maintenance Phase 1 will be randomized 1:1 to receive rifaximin 550 mg TID or placebo TID for 2 weeks with a 2 week treatment-free follow-up.

- **Maintenance Phase 2 (8 Weeks) -** Responders in the Double-Blind, Randomized (first repeat) Treatment Phase will be eligible for Maintenance Phase 2 and will continue with an additional treatment-free follow-up period of up to 8 weeks. Subjects who experience recurrence will immediately be transitioned into the Second Repeat Treatment Phase. Subjects who do not meet recurrence criteria by the end of the 8-week Maintenance Phase 2 will be withdrawn from the study.

- **Second Repeat Treatment Phase (4 Weeks) and End of Study** - Subjects with recurrence in Maintenance Phase 2 will be eligible to enter the Second Repeat Treatment Phase, and will receive a second repeat treatment of rifaximin 550 mg TID or placebo TID for 2 weeks with a 2 week treatment-free follow-up. The treatment assignment from the Double-Blind, Randomized (first repeat) Treatment Phase will be maintained in this phase. At the end of this phase, subjects will undergo end of study assessments.

8.3.1. Subject Population

Patients selected for inclusion will meet the Rome III diagnostic criteria for IBS-D. The Rome III criteria are the accepted current standard for diagnosing IBS in the clinical setting and are consistent with FDA guidance. Table 20 outlines the criteria for diagnosing and subtyping IBS using Rome III.

Additionally, during the diary eligibility period, the following average daily symptom scores for IBS are required in all categories for entry into the proposed study designs:

- An average score ≥ 3 for abdominal pain (Scale: 0-10, with 0 indicating no pain, and 10 indicating the worst imaginable pain).
- An average score ≥ 3 for bloating (Scale: 0-6, ranking how bothersome IBS-related bloating was in the last 24 hours, 0 = not at all; 1 = hardly; 2 = somewhat; 3 = moderately; 4 = a good deal; 5 = a great deal; 6 = a very great deal.”)

- A score of 6 or greater for stool consistency using the Bristol Stool form Scale for at least 2 out of 7 days (Note: Subjects will not be eligible for the study if they experience hard or lumpy stools [Bristol Scale Type 1 or 2, consistent with constipation], during the eligibility period.)

Subjects will record IBS symptoms in an IVRS during screening to confirm eligibility and will have had a colonoscopy within the last 2 years to rule out inflammatory bowel diseases or other causes of IBS symptoms. Other confounding medical conditions and medications will be excluded by qualified healthcare professionals.

Table 20 Rome III: IBS Diagnosis and Subtyping

Rome III Criteria
Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months, with symptom onset at least 6 months prior to diagnosis associated with 2 or more of the following: improvement with defecation; onset associated with a change in frequency of stool; and/or onset associated with a change in form (appearance) of stool.
Rome III Subtyping
1. IBS with constipation (IBS-C) – hard or lumpy stools[a] ≥ 25% and loose (mushy) or watery stools[b] < 25% of bowel movements, in the absence of use of antidiarrheals or laxatives.
2. IBS with diarrhea (IBS-D) – loose (mushy) or watery stools[b] ≥ 25% and hard or lumpy stool[a] < 25% of bowel movements, in the absence of use of antidiarrheals or laxatives.
3. Mixed IBS (IBS-M) – hard or lumpy stools[a] ≥ 25% and loose (mushy) or watery stools[b] ≥ 25% of bowel movements, in the absence of use of antidiarrheals or laxatives.
4. Unsubtyped IBS (IBS-U) – insufficient abnormality of stool consistency to meet criteria for IBS-C, -D or -M.

References: Ersryd et al.,[89] Corazziari et al.,[90] and Thompson et al.[91]
a. Bristol Stool Form Scale 1–2 [separate hard lumps like nuts (difficult to pass) or sausage shaped but lumpy].
b. Bristol Stool Form Scale 6–7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid).

8.3.2. Repeat Treatment Study Objectives and Endpoints

The primary objective of this study is to evaluate the efficacy of repeat treatment with rifaximin 550 mg TID for 2 weeks in subjects with non-C IBS who responded to an initial course of rifaximin treatment and subsequently experienced recurrence.

The **Primary Endpoint** is the proportion of subjects who are responders to repeat treatment in both IBS-related abdominal pain AND stool consistency during the 2 weeks treatment; 2-week treatment-free follow-up during the Double-Blind, Randomized (first repeat) Treatment Phase.

Weekly response for the primary endpoint is defined based on IBS-symptom related questions, as follows:

- Weekly treatment success in IBS-related abdominal pain is defined as a 30% or greater improvement from baseline in the weekly average abdominal pain score, based on subject response to the following daily question:

  "In regards to your specific IBS symptom of abdominal pain, on a scale of 0-10, what was your worst IBS-related abdominal pain in the last 24 hours? 'Zero' means you have no pain at all; 'Ten' means the worst possible pain you can imagine."

- Weekly treatment success in stool consistency is achieved when a subject has 50% reduction in the number of stools scored at ≥ 6 over 7 days as compared to baseline based on subject response to the following daily question based on the Bristol Stool Form Scale:

  "On a scale of 1-7, what was the overall form of your bowel movements in the last 24 hours? 1 = Separate hard lumps, like nuts (hard to pass); 2 = Sausage-shaped but lumpy; 3 = Like a sausage but with cracks on its surface; 4 = Like a sausage or snake, smooth and soft; 5 = Soft blobs with clear cut edges (passed easily); 6 = Fluffy pieces with ragged edges, a mushy stool; 7 = Watery stool, no solid pieces; entirely liquid."

Secondary Endpoints for the study, during the Double-blind, Randomized (first repeat) Treatment phase, are as follows:

- The proportion of subjects who are responders during the 2-weeks treatment; 2-weeks treatment-free follow-up periods for the following: IBS-related abdominal pain; stool consistency; IBS-related bloating; and IBS symptoms (daily reported).
- Change from baseline to each week for the following: abdominal pain (11 point scoring system, *see above*); stool consistency (7-point scoring system, Bristol Stool form Scale, *see above*); Bloating (7-point scoring system); IBS symptoms (7-point scoring system); sense of urgency (based on a Yes/No diary question).
- The number of recurrent events relative to person-time on study in IBS-related abdominal pain and stool consistency during the Double-Blind, Randomized (first repeat) Treatment Phase and through the follow-up 8-week Maintenance phase.

Weekly treatment success for IBS-related bloating is assessed using the following question: *"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; 1 = hardly; 2 = somewhat; 3 = moderately; 4 = a good deal; 5 = a great deal; 6 = a very great deal."* Treatment success for bloating is achieved when a subject rates his/her daily IBS-related bloating as either: 0 (not at all) or 1(hardly) at least 50% of the days in a given week; OR 0 (not at all), 1 (hardly) or 2 (somewhat) 100% of the days in a given week

Weekly treatment success for IBS symptoms (daily reported) is assessed using the following question: *"In regards to all of your symptoms of IBS, on a scale of 0-6, how bothersome were your symptoms of IBS in the last 24 hours? 0 = not at all; 1 = hardly; 2 = somewhat; 3 = moderately; 4 = a good deal; 5 = a great deal; 6 = a very great deal."* Treatment success for IBS symptoms is achieved when a subject rates his/her daily IBS symptoms as either: 0 (not at all) or 1(hardly) at least 50% of the days in a given week; OR 0 (not at all), 1 (hardly) or 2 (somewhat) 100% of the days in a given week.

Planned **Exploratory Endpoints** for the study include the following:

- Descriptive characterization of the proportion of responders (yes/no) on rifaximin after the Double-Blind, Randomized (first repeat) Treatment Phase versus their response profile (yes/no) in the Second Repeat Treatment Phase.
- Biomarker assessments (to be determined).

Safety Endpoints will include monitoring and assessment of AEs, clinical laboratory parameters, vital signs, and physical examinations.

8.3.3. Analysis Populations and Efficacy Endpoints

Three analysis populations are planned for efficacy assessments:

- The ITT population will include all randomized subjects who ingested at least one dose of the study drug.
- The Double-Blind, Randomized (first repeat) Treatment population will include subjects who responded to the initial treatment and who were randomized and received at least one dose of the study drug in the First Re-treatment Phase. This will serve as the primary analysis population.
- The Second Repeat Treatment population will include subjects who responded to the initial repeat treatment and received at least one dose of the study drug in the Second Re-treatment Phase.

The primary efficacy analysis will be conducted on the Double-Blind, Randomized (first repeat) Treatment population and will be conducted at the end of the Double-Blind, Randomized (first repeat) Treatment Phase. The analysis will utilize Cochran-Mantel-Haenszel method adjusting for analysis center (PROC FREQ in SAS/STAT). Weekly response will be set to non-response when the subject completes <4 diary days.

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Appendix 1 - XIFAXAN® Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIFAXAN safely and effectively. See full prescribing information for XIFAXAN.

XIFAXAN® (rifaximin) Tablets
Initial U.S. Approval: 2004

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN and other antibacterial drugs, XIFAXAN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

---------- **RECENT MAJOR CHANGES** ----------

Indications and Usage, Hepatic Encephalopathy (1.2)	03/2010
Dosage and Administration, Hepatic Encephalopathy (2.2)	03/2010

---------- **INDICATIONS AND USAGE** ----------

XIFAXAN is a rifamycin antibacterial indicated for:

- The treatment of patients (≥ 12 years of age) with travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli* (1.1)
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age (1.2)

Limitations of Use

- TD: Do not use in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli* (1.1)

---------- **DOSAGE AND ADMINISTRATION** ----------

- Travelers' diarrhea: One 200 mg tablet taken orally three times a day for 3 days, with or without food (2.1)
- Hepatic encephalopathy: One 550 mg tablet taken orally two times a day, with or without food (2.2)

---------- **DOSAGE FORMS AND STRENGTHS** ----------

- 200 mg and 550 mg tablets (3)

---------- **CONTRAINDICATIONS** ----------

History of hypersensitivity to rifaximin, rifamycin antimicrobial agents, or any of the components of XIFAXAN (4.1)

---------- **WARNINGS AND PRECAUTIONS** ----------

- Travelers' Diarrhea Not Caused by *E. coli*: XIFAXAN was not effective in diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *E. coli*. If diarrhea symptoms get worse or persist for more than 24-48 hours, discontinue XIFAXAN and consider alternative antibiotics (5.1)
- *Clostridium difficile*-Associated Diarrhea: Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy (5.2)
- Hepatic Impairment: Use with caution in patients with severe (Child-Pugh C) hepatic impairment (5.4, 8.7)

---------- **ADVERSE REACTIONS** ----------

- Most common adverse reactions in travelers' diarrhea (≥ 5%): Flatulence, headache, abdominal pain, rectal tenesmus, defecation urgency and nausea (6.1)
- Most common adverse reactions in HE (≥ 10%): Peripheral edema, nausea, dizziness, fatigue, ascites, flatulence, and headache (6.1)

To report suspected adverse reactions, contact Salix Pharmaceuticals at 1-866-669-7597 and www.Salix.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

---------- **USE IN SPECIFIC POPULATIONS** ----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue nursing or drug, taking into account the importance of the drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: Nov/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Travelers' Diarrhea
1.2 Hepatic Encephalopathy
2 DOSAGE AND ADMINISTRATION
2.1 Dosage for Travelers' Diarrhea
2.2 Dosage for Hepatic Encephalopathy
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Hypersensitivity
5 WARNINGS AND PRECAUTIONS
5.1 Travelers' Diarrhea Not Caused by *Escherichia coli*
5.2 *Clostridium difficile*-Associated Diarrhea
5.3 Development of Drug Resistant Bacteria
5.4 Severe (Child-Pugh C) Hepatic Impairment
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Travelers' Diarrhea
14.2 Hepatic Encephalopathy
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Persistent Diarrhea
17.2 *Clostridium difficile*-Associated Diarrhea
17.3 Administration with Food
17.4 Antibacterial Resistance
17.5 Severe Hepatic Impairment

* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN and other antibacterial drugs, XIFAXAN when used to treat infection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

1.1 Travelers' Diarrhea

XIFAXAN 200 mg is indicated for the treatment of patients (≥ 12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* [*see Warnings and Precautions (5)*, *Clinical Pharmacology (12.4)* and *Clinical Studies (14.1)*].

Limitations of Use

XIFAXAN should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

1.2 Hepatic Encephalopathy

XIFAXAN 550 mg is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.

In the trials of XIFAXAN for HE, 91% of the patients were using lactulose concomitantly. Differences in the treatment effect of those patients not using lactulose concomitantly could not be assessed.

XIFAXAN has not been studied in patients with MELD (Model for End-Stage Liver Disease) scores > 25, and only 8.6% of patients in the controlled trial had MELD scores over 19. There is increased systemic exposure in patients with more severe hepatic dysfunction [*see Warnings and Precautions (5.4), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Travelers' Diarrhea

The recommended dose of XIFAXAN is one 200 mg tablet taken orally three times a day for 3 days. XIFAXAN can be administered orally, with or without food [*see Clinical Pharmacology (12.3)*].

2.2 Dosage for Hepatic Encephalopathy

The recommended dose of XIFAXAN is one 550 mg tablet taken orally two times a day, with or without food [*see Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

XIFAXAN is a pink-colored biconvex tablet and is available in the following strengths:

- 200 mg – a round tablet debossed with "Sx" on one side.
- 550 mg – an oval tablet debossed with "rfx" on one side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Travelers' Diarrhea Not Caused by *Escherichia coli*

XIFAXAN was not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*.

Discontinue XIFAXAN if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

XIFAXAN is not effective in cases of travelers' diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. XIFAXAN should not be used in patients where *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.

5.2 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Development of Drug Resistant Bacteria

Prescribing XIFAXAN for travelers' diarrhea in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.4 Severe (Child-Pugh C) Hepatic Impairment

There is increased systemic exposure in patients with severe hepatic impairment. Animal toxicity studies did not achieve systemic exposures that were seen in patients with severe hepatic impairment. The clinical trials were limited to patients with MELD scores < 25. Therefore, caution should be exercised when administering XIFAXAN to patients with severe hepatic impairment (Child-Pugh C) [*see Use in Specific Populations (8.7), Nonclinical Toxicology (13.2) and Clinical Studies (14.2)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Travelers' Diarrhea

The safety of XIFAXAN 200 mg taken three times a day was evaluated in patients with travelers' diarrhea consisting of 320 patients in two placebo-controlled clinical trials with 95% of patients receiving three or four days of treatment with XIFAXAN. The population studied had a mean age of 31.3 (18-79) years of which approximately 3% were ≥ 65 years old, 53% were male and 84% were White, 11% were Hispanic.

Discontinuations due to adverse reactions occurred in 0.4% of patients. The adverse reactions leading to discontinuation were taste loss, dysentery, weight decrease, anorexia, nausea and nasal passage irrigation.

All adverse reactions for XIFAXAN 200 mg three times daily that occurred at a frequency ≥ 2% in the two placebo-controlled trials combined are provided in Table 1. (These include adverse reactions that may be attributable to the underlying disease.)

Table 1. All Adverse Reactions With an Incidence ≥ 2% Among Patients Receiving XIFAXAN Tablets, 200 mg Three Times Daily, in Placebo-Controlled Studies

	Number (%) of Patients	
MedDRA Preferred Term	XIFAXAN Tablets, 600 mg/day N = 320	Placebo N = 228
Flatulence	36 (11%)	45 (20%)
Headache	31 (10%)	21 (9%)
Abdominal pain NOS*	23 (7%)	23 (10%)
Rectal tenesmus	23 (7%)	20 (9%)
Defecation urgency	19 (6%)	21 (9%)
Nausea	17 (5%)	19 (8%)
Constipation	12 (4%)	8 (4%)
Pyrexia	10 (3%)	10 (4%)
Vomiting NOS	7 (2%)	4 (2%)

*NOS: Not otherwise specified

The following adverse reactions, presented by body system, have also been reported in < 2% of patients taking XIFAXAN in the two placebo-controlled clinical trials where the 200 mg tablet was taken three times a day for travelers' diarrhea. The following includes adverse reactions regardless of causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Lymphocytosis, monocytosis, neutropenia

Ear and Labyrinth Disorders: Ear pain, motion sickness, tinnitus

Gastrointestinal Disorders: Abdominal distension, diarrhea NOS, dry throat, fecal abnormality NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort

General Disorders and Administration Site Conditions: Chest pain, fatigue, malaise, pain NOS, weakness

Infections and Infestations: Dysentery NOS, respiratory tract infection NOS, upper respiratory tract infection NOS

Injury and Poisoning: Sunburn

Investigations: Aspartate aminotransferase increased, blood in stool, blood in urine, weight decreased

Metabolic and Nutritional Disorders: Anorexia, dehydration

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, muscle spasms, myalgia, neck pain

Nervous System Disorders: Abnormal dreams, dizziness, migraine NOS, syncope, loss of taste

Psychiatric Disorders: Insomnia

Renal and Urinary Disorders: Choluria, dysuria, hematuria, polyuria, proteinuria, urinary frequency

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea NOS, nasal passage irritation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea

Skin and Subcutaneous Tissue Disorders: Clamminess, rash NOS, sweating increased

Vascular Disorders: Hot flashes NOS

Hepatic Encephalopathy

The data described below reflect exposure to XIFAXAN 550 mg in 348 patients, including 265 exposed for 6 months and 202 exposed for more than a year (mean exposure was 364 days). The safety of XIFAXAN 550 mg taken two times a day for reducing the risk of overt hepatic encephalopathy recurrence in adult patients was evaluated in a 6-month placebo-controlled clinical trial (n = 140) and in a long term follow-up study (n = 280). The population studied had a mean age of 56.26 (range: 21-82) years; approximately 20% of the patients were ≥ 65 years old, 61% were male, 86% were White, and 4% were Black. Ninety-one percent of patients in the trial were taking lactulose concomitantly. All adverse reactions that occurred at an incidence ≥ 5% and at a higher incidence in XIFAXAN 550 mg-treated subjects than in the placebo group in the 6-month trial are provided in Table 2. (These include adverse events that may be attributable to the underlying disease).

Table 2. Adverse Reactions Occurring in ≥ 5% of Patients Receiving XIFAXAN and at a Higher Incidence Than Placebo

	Number (%) of Patients	
MedDRA Preferred Term	XIFAXAN Tablets 550 mg TWICE DAILY N = 140	Placebo N = 159
Edema peripheral	21 (15%)	13 (8%)
Nausea	20 (14%)	21 (13%)
Dizziness	18 (13%)	13 (8%)
Fatigue	17 (12%)	18 (11%)
Ascites	16 (11%)	15 (9%)
Muscle spasms	13 (9%)	11 (7%)
Pruritus	13 (9%)	10 (6%)
Abdominal pain	12 (9%)	13 (8%)
Abdominal distension	11 (8%)	12 (8%)
Anemia	11 (8%)	6 (4%)
Cough	10 (7%)	11 (7%)
Depression	10 (7%)	8 (5%)
Insomnia	10 (7%)	11 (7%)
Nasopharyngitis	10 (7%)	10 (6%)
Abdominal pain upper	9 (6%)	8 (5%)
Arthralgia	9 (6%)	4 (3%)
Back pain	9 (6%)	10 (6%)
Constipation	9 (6%)	10 (6%)
Dyspnea	9 (6%)	7 (4%)
Pyrexia	9 (6%)	5 (3%)
Rash	7 (5%)	6 (4%)

The following adverse reactions, presented by body system, have also been reported in the placebo-controlled clinical trial in greater than 2% but less than 5% of patients taking XIFAXAN 550 mg taken orally two times a day for hepatic encephalopathy. The following includes adverse events occurring at a greater incidence than placebo, regardless of causal relationship to drug exposure.

Ear and Labyrinth Disorders: Vertigo

Gastrointestinal Disorders: Abdominal pain lower, abdominal tenderness, dry mouth, esophageal variceal bleed, stomach discomfort

General Disorders and Administration Site Conditions: Chest pain, generalized edema, influenza like illness, pain NOS

Infections and Infestations: Cellulitis, pneumonia, rhinitis, upper respiratory tract infection NOS

Injury, Poisoning and Procedural Complications: Contusion, fall, procedural pain

Investigations: Weight increased

Metabolic and Nutritional Disorders: Anorexia, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hyponatremia

Musculoskeletal, Connective Tissue, and Bone Disorders: Myalgia, pain in extremity

Nervous System Disorders: Amnesia, disturbance in attention, hypoesthesia, memory impairment, tremor

Psychiatric Disorders: Confusional state

Respiratory, Thoracic, and Mediastinal Disorders: Epistaxis

Vascular Disorders: Hypotension

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of XIFAXAN. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to XIFAXAN.

Infections and Infestations

Cases of *C. difficile*-associated colitis have been reported [*see Warnings and Precautions (5.2)*].

General

Hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, pruritus and anaphylaxis have been reported. These events occurred as early as within 15 minutes of drug administration.

7 DRUG INTERACTIONS

In vitro studies have shown that rifaximin did not inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 at concentrations ranging from 2 to 200 ng/mL [*see Clinical Pharmacology (12.3)*]. Rifaximin is not expected to inhibit these enzymes in clinical use.

An *in vitro* study has suggested that rifaximin induces CYP3A4 [*see Clinical Pharmacology (12.3)*]. However, in patients with normal liver function, rifaximin at the recommended dosing regimen is not expected to induce CYP3A4. It is unknown whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function who have elevated rifaximin concentrations.

An *in vitro* study suggested that rifaximin is a substrate of P-glycoprotein. It is unknown whether concomitant drugs that inhibit P-glycoprotein can increase the systemic exposure of rifaximin [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. Rifaximin has been shown to be teratogenic in rats and rabbits at doses that caused maternal toxicity. XIFAXAN tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of rifaximin to pregnant rats and rabbits at dose levels that caused reduced body weight gain resulted in eye malformations in both rat and rabbit fetuses. Additional malformations were observed in fetal rabbits that included cleft palate, lumbar scoliosis, brachygnathia, interventricular septal defect, and large atrium.

The fetal rat malformations were observed in a study of pregnant rats administered a high dose that resulted in 16 times the therapeutic dose to diarrheic patients or 1 times the therapeutic dose to patients with hepatic encephalopathy (based upon plasma AUC comparisons). Fetal rabbit malformations were observed from pregnant rabbits administered mid and high doses that resulted in 1 or 2 times the therapeutic dose to diarrheic patients or less than 0.1 times the dose in patients with hepatic encephalopathy, based upon plasma AUC comparisons.

Post-natal developmental effects were not observed in rat pups from pregnant/lactating female rats dosed during the period from gestation to Day 20 post-partum at the highest dose which resulted in approximately 16 times the human therapeutic dose for travelers' diarrhea (based upon AUCs) or approximately 1 times the AUCs derived from therapeutic doses to patients with hepatic encephalopathy.

8.3 Nursing Mothers

It is not known whether rifaximin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from XIFAXAN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of XIFAXAN 200 mg in pediatric patients with travelers' diarrhea less than 12 years of age have not been established.

The safety and effectiveness of XIFAXAN 550 mg for HE have not been established in patients < 18 years of age.

8.5 Geriatric Use

Clinical studies with rifaximin 200 mg for travelers' diarrhea did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects.

In the controlled trial with XIFAXAN 550 mg for hepatic encephalopathy, 19.4% were 65 and over, while 2.3% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

8.7 Hepatic Impairment

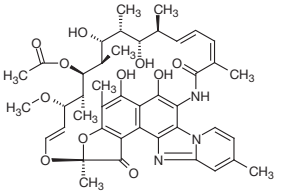
Following administration of XIFAXAN 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure (i.e., AUC_{τ}) of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. No dosage adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when XIFAXAN is administered to patients with severe hepatic impairment [*see Warnings and Precautions (5.4), Clinical Pharmacology (12.3), Nonclinical Toxicology (13.2), and Clinical Studies (14.2)*].

10 OVERDOSAGE

No specific information is available on the treatment of overdosage with XIFAXAN. In clinical studies at doses higher than the recommended dose (> 600 mg/day for travelers' diarrhea or > 1100 mg/day for hepatic encephalopathy), adverse reactions were similar in subjects who received doses higher than the recommended dose and placebo. In the case of overdosage, discontinue XIFAXAN, treat symptomatically, and institute supportive measures as required.

11 DESCRIPTION

XIFAXAN tablets contain rifaximin, a non-aminoglycoside semi-synthetic, nonsystemic antibiotic derived from rifamycin SV. Rifaximin is a structural analog of rifampin. The chemical name for rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-e]pyrido[1,2-á]-benzimidazole-1,15(2*H*)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$ and its molecular weight is 785.9. The chemical structure is represented below:



XIFAXAN tablets for oral administration are film-coated and contain 200 mg or 550 mg of rifaximin.

Inactive ingredients: Each tablet contains colloidal silicon dioxide, disodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rifaximin is an antibacterial drug [*see Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Absorption

Travelers' Diarrhea

Systemic absorption of rifaximin (200 mg three times daily) was evaluated in 13 subjects challenged with shigellosis on Days 1 and 3 of a three-day course of treatment. Rifaximin plasma concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81 to 3.4 ng/mL on Day 1 and 0.68 to 2.26 ng/mL on Day 3. Similarly, $AUC_{0\text{-last}}$ estimates were 6.95 ± 5.15 ng•h/mL on Day 1 and 7.83 ± 4.94 ng•h/mL on Day 3. XIFAXAN is not suitable for treating systemic bacterial infections because of limited systemic exposure after oral administration [*see Warnings and Precautions (5.1)*].

Hepatic Encephalopathy

After a single dose and multiple doses of rifaximin 550 mg in healthy subjects, the mean time to reach peak plasma concentrations was about an hour. The pharmacokinetic (PK) parameters were highly variable and the accumulation ratio based on AUC was 1.37.

The PK of rifaximin in patients with a history of HE was evaluated after administration of XIFAXAN, 550 mg two times a day. The PK parameters were associated with a high variability and mean rifaximin exposure (AUC_τ) in patients with a history of HE (147 ng•h/mL) was approximately 12-fold higher than that observed in healthy subjects following the same dosing regimen (12.3 ng•h/mL). When PK parameters were analyzed based on Child-Pugh Class A, B, and C, the mean AUC_τ was 10-, 13-, and 20-fold higher, respectively, compared to that in healthy subjects (Table 3).

Table 3. Mean (± SD) Pharmacokinetic Parameters of Rifaximin at Steady-State in Patients with a History of Hepatic Encephalopathy by Child-Pugh Class[1]

	Healthy Subjects (n = 14)	Child-Pugh Class		
		A (n = 18)	B (n = 7)	C (n = 4)
AUC_{tau} (ng•h/mL)	12.3 ± 4.8	118 ± 67.8	161 ± 101	246 ± 120
C_{max} (ng/mL)	3.4 ± 1.6	19.5 ± 11.4	25.1 ± 12.6	35.5 ± 12.5
T_{max}[2] (h)	0.8 (0.5, 4.0)	1 (0.9, 10)	1 (0.97, 1)	1 (0, 2)

[1] Cross-study comparison with PK parameters in healthy subjects
[2] Median (range)

Food Effect in Healthy Subjects

A high-fat meal consumed 30 minutes prior to XIFAXAN dosing in healthy subjects delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased the systemic exposure (AUC) of rifaximin by 2-fold (Table 4).

Table 4. Mean (± SD) Pharmacokinetic Parameters After Single-Dose Administration of XIFAXAN Tablets 550 mg in Healthy Subjects Under Fasting and Fed Conditions (N = 12)

Parameter	Fasting	Fed
C_{max} (ng/mL)	4.1 ± 1.5	4.8 ± 4.3
T_{max}[1] (h)	0.8 (0.5, 2.1)	1.5 (0.5, 4.1)
Half-Life (h)	1.8 ± 1.4	4.8 ± 1.3
AUC (ng•h/mL)	11.1 ± 4.2	22.5 ± 12

[1] Median (range)

XIFAXAN can be administered with or without food [*see Dosage and Administration (2.1 and 2.2)*].

Distribution

Rifaximin is moderately bound to human plasma proteins. *In vivo*, the mean protein binding ratio was 67.5% in healthy subjects and 62% in patients with hepatic impairment when XIFAXAN 550 mg was administered.

Metabolism and Excretion

In a mass balance study, after administration of 400 mg ^{14}C-rifaximin orally to healthy volunteers, of the 96.94% total recovery, 96.62% of the administered radioactivity was recovered in feces almost exclusively as the unchanged drug and 0.32% was recovered in urine mostly as metabolites with 0.03% as the unchanged drug. Rifaximin accounted for 18% of radioactivity in plasma. This suggests that the absorbed rifaximin undergoes metabolism with minimal renal excretion of the unchanged drug. The enzymes responsible for metabolizing rifaximin are unknown.

In a separate study, rifaximin was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa, suggesting biliary excretion of rifaximin.

Specific Populations

Hepatic Impairment

The systemic exposure of rifaximin was markedly elevated in patients with hepatic impairment compared to healthy subjects. The mean AUC in patients with Child-Pugh Class C hepatic impairment was 2-fold higher than in patients with Child-Pugh Class A hepatic impairment (see Table 3), [*see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)*].

Renal Impairment

The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

Drug Interactions

In vitro drug interaction studies have shown that rifaximin, at concentrations ranging from 2 to 200 ng/mL, did not inhibit human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4.

In an *in vitro* study, rifaximin was shown to induce CYP3A4 at the concentration of 0.2 µM.

An *in vitro* study suggests that rifaximin is a substrate of P-glycoprotein. In the presence of P-glycoprotein inhibitor verapamil, the efflux ratio of rifaximin was reduced greater than 50% *in vitro*. The effect of P-glycoprotein inhibition on rifaximin was not evaluated *in vivo*.

The inhibitory effect of rifaximin on P-gp transporter was observed in an *in vitro* study. The effect of rifaximin on P-gp transporter was not evaluated *in vivo*.

Midazolam

The effect of rifaximin 200 mg administered orally every 8 hours for 3 days and for 7 days on the pharmacokinetics of a single dose of either midazolam 2 mg intravenous or midazolam 6 mg orally was evaluated in healthy subjects. No significant difference was observed in the metrics of systemic exposure or elimination of intravenous or oral midazolam or its major metabolite, 1'-hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity for the 200 mg three times a day dosing regimen.

After XIFAXAN 550 mg was administered three times a day for 7 days and 14 days to healthy subjects, the mean AUC of single midazolam 2 mg orally was 3.8% and 8.8% lower, respectively, than when midazolam was administered alone. The mean C_{max} of midazolam was also decreased by 4-5% when XIFAXAN was administered for 7-14 days prior to midazolam administration. This degree of interaction is not considered clinically meaningful.

The effect of rifaximin on CYP3A4 in patients with impaired liver function who have elevated systemic exposure is not known.

Oral Contraceptives Containing 0.07 mg Ethinyl Estradiol and 0.5 mg Norgestimate

The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if rifaximin 200 mg orally administered three times a day for 3 days (the dosing regimen for travelers' diarrhea) altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.5 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin [*see Drug Interactions (7)*].

Effect of rifaximin on oral contraceptives was not studied for XIFAXAN 550 mg twice a day, the dosing regimen for hepatic encephalopathy.

12.4 Microbiology

Mechanism of Action

Rifaximin is a non-aminoglycoside semi-synthetic antibacterial derived from rifamycin SV. Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied.

Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Rifaximin has been shown to be active against the following pathogen in clinical studies of infectious diarrhea as described in the *Indications and Usage (1)* section: *Escherichia coli* (enterotoxigenic and enteroaggregative strains).

For HE, rifaximin is thought to have an effect on the gastrointestinal flora.

Susceptibility Tests

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A6 [*see References (15)*]. However, the correlation between susceptibility testing and clinical outcome has not been determined.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Malignant schwannomas in the heart were significantly increased in male Crl:CD® (SD) rats that received rifaximin by oral gavage for two years at 150 to 250 mg/kg/day (doses equivalent to 2.4 to 4 times the recommended dose of 200 mg three times daily for travelers' diarrhea, and equivalent to 1.3 to 2.2 times the recommended dose of 550 mg twice daily for hepatic encephalopathy, based on relative body surface area comparisons). There was no increase in tumors in Tg.rasH2 mice dosed orally with rifaximin for 26 weeks at 150 to 2000 mg/kg/day (doses equivalent to 1.2 to 16 times the recommended daily dose for travelers' diarrhea and equivalent to 0.7 to 9 times the recommended daily dose for hepatic encephalopathy, based on relative body surface area comparisons).

Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal aberration assay, rat bone marrow micronucleus assay, rat hepatocyte unscheduled DNA synthesis assay, or the CHO/HGPRT mutation assay. There was no effect on fertility in male or female rats following the administration of rifaximin at doses up to 300 mg/kg (approximately 5 times the clinical dose of 600 mg/day, and approximately 2.6 times the clinical dose of 1100 mg/day, adjusted for body surface area).

13.2 Animal Toxicology and/or Pharmacology

Oral administration of rifaximin for 3-6 months produced hepatic proliferation of connective tissue in rats (50 mg/kg/day) and fatty degeneration of liver in dogs (100 mg/kg/day). However, plasma drug levels were not measured in these studies. Subsequently, rifaximin was studied at doses as high as 300 mg/kg/day in rats for 6 months and 1000 mg/kg/day in dogs for 9 months, and no signs of hepatotoxicity were observed. The maximum plasma $AUC_{0\text{-}8\ hr}$ values from the 6 month rat and 9 month dog toxicity studies (range: 42-127 ng•h/mL) was lower than the maximum plasma $AUC_{0\text{-}8\ hr}$ values in cirrhotic patients (range: 19-306 ng•h/mL).

14 CLINICAL STUDIES

14. 1 Travelers' Diarrhea

The efficacy of XIFAXAN given as 200 mg orally taken three times a day for 3 days was evaluated in 2 randomized, multi-center, double-blind, placebo-controlled studies in adult subjects with travelers' diarrhea. One study was conducted at clinical sites in Mexico, Guatemala, and Kenya (Study 1). The other study was conducted in Mexico, Guatemala, Peru, and India (Study 2). Stool specimens were collected before treatment and 1 to 3 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both studies was *Escherichia coli*.

The clinical efficacy of XIFAXAN was assessed by the time to return to normal, formed stools and resolution of symptoms. The primary efficacy endpoint was time to last unformed stool (TLUS) which was defined as the time to the last unformed stool passed, after which clinical cure was declared. Table 5 displays the median TLUS and the number of patients who achieved clinical cure for the intent to treat (ITT) population of Study 1. The duration of diarrhea was significantly shorter in patients treated with XIFAXAN than in the placebo group. More patients treated with XIFAXAN were classified as clinical cures than were those in the placebo group.

Table 5. Clinical Response in Study 1 (ITT population)

	XIFAXAN (n=125)	Placebo (n=129)	Estimate (97.5% CI)	P-Value
Median TLUS (hours)	32.5	58.6	1.78[a] (1.26, 2.50)	0.0002
Clinical cure, n (%)	99 (79.2)	78 (60.5)	18.7[b] (5.3, 32.1)	0.001

[a] Hazard Ratio
[b] Difference in rates

Microbiological eradication (defined as the absence of a baseline pathogen in culture of stool after 72 hours of therapy) rates for Study 1 are presented in Table 6 for patients with any pathogen at baseline and for the subset of patients with *Escherichia coli* at baseline. *Escherichia coli* was the only pathogen with sufficient numbers to allow comparisons between treatment groups.

Even though XIFAXAN had microbiologic activity similar to placebo, it demonstrated a clinically significant reduction in duration of diarrhea and a higher clinical cure rate than placebo. Therefore, patients should be managed based on clinical response to therapy rather than microbiologic response.

Table 6. Microbiologic Eradication Rates in Study 1 Subjects with a Baseline Pathogen

	XIFAXAN	Placebo
Overall	48/70 (68.6)	41/61 (67.2)
E. coli	38/53 (71.7)	40/54 (74.1)

The results of Study 2 supported the results presented for Study 1. In addition, this study provided evidence that subjects treated with XIFAXAN with fever and/or blood in the stool at baseline had prolonged TLUS. These subjects had lower clinical cure rates than those without fever or blood in the stool at baseline. Many of the patients with fever and/or blood in the stool (dysentery-like diarrheal syndromes) had invasive pathogens, primarily *Campylobacter jejuni*, isolated in the baseline stool.

Also in this study, the majority of the subjects treated with XIFAXAN who had *Campylobacter jejuni* isolated as a sole pathogen at baseline failed treatment and the resulting clinical cure rate for these patients was 23.5% (4/17). In addition to not being different from placebo, the microbiologic eradication rates for subjects with *Campylobacter jejuni* isolated at baseline were much lower than the eradication rates seen for *Escherichia coli*.

In an unrelated open-label, pharmacokinetic study of oral XIFAXAN 200 mg taken every 8 hours for 3 days, 15 adult subjects were challenged with *Shigella flexneri* 2a, of whom 13 developed diarrhea or dysentery and were treated with XIFAXAN. Although this open-label challenge trial was not adequate to assess the effectiveness of XIFAXAN in the treatment of shigellosis, the following observations were noted: eight subjects received rescue treatment with ciprofloxacin either because of lack of response to XIFAXAN treatment within 24 hours (2), or because they developed severe dysentery (5), or because of recurrence of *Shigella flexneri* in the stool (1); five of the 13 subjects received ciprofloxacin although they did not have evidence of severe disease or relapse.

14.2 Hepatic Encephalopathy

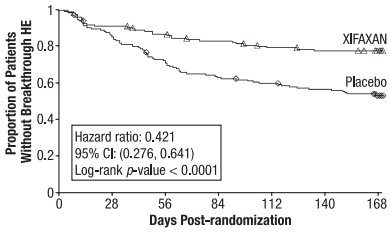
The efficacy of XIFAXAN 550 mg taken orally two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult subjects from the U.S., Canada and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE). Eligible subjects had ≥ 2 episodes of HE associated with chronic liver disease in the previous 6 months.

A total of 299 subjects were randomized to receive either XIFAXAN (n=140) or placebo (n=159) in this study. Patients had a mean age of 56 years (range, 21-82 years), 81% < 65 years of age, 61% were male and 86% White. At baseline, 67% of patients had a Conn score of 0 and 68% had an asterixis grade of 0. Patients had MELD scores of either ≤ 10 (27%) or 11 to 18 (64%) at baseline. No patients were enrolled with a MELD score of > 25. Nine percent of the patients were Child-Pugh Class C. Lactulose was concomitantly used by 91% of the patients in each treatment arm of the study. Per the study protocol, patients were withdrawn from the study after experiencing a breakthrough HE episode. Other reasons for early study discontinuation included: adverse reactions (XIFAXAN 6%; placebo 4%), patient request to withdraw (XIFAXAN 4%; placebo 6%) and other (XIFAXAN 7%; placebo 5%).

The primary endpoint was the time to first breakthrough overt HE episode. A breakthrough overt HE episode was defined as a marked deterioration in neurological function and an increase of Conn score to Grade ≥ 2. In patients with a baseline Conn score of 0, a breakthrough overt HE episode was defined as an increase in Conn score of 1 and asterixis grade of 1.

Breakthrough overt HE episodes were experienced by 31 of 140 subjects (22%) in the XIFAXAN group and by 73 of 159 subjects (46%) in the placebo group during the 6-month treatment period. Comparison of Kaplan-Meier estimates of event-free curves showed XIFAXAN significantly reduced the risk of HE breakthrough by 58% during the 6-month treatment period. Presented below in Figure 1 is the Kaplan-Meier event-free curve for all subjects (n = 299) in the study.

Figure 1: Kaplan-Meier Event-Free Curves[1] in HE Study (Time to First Breakthrough-HE Episode up to 6 Months of Treatment, Day 170) (ITT Population)

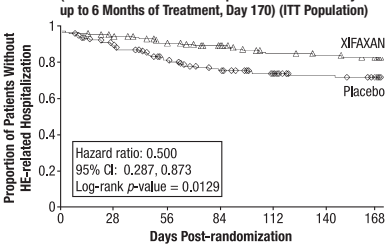


Note: Open diamonds and open triangles represent censored subjects.
[1] Event-free refers to non-occurrence of breakthrough HE.

When the results were evaluated by the following demographic and baseline characteristics, the treatment effect of XIFAXAN 550 mg in reducing the risk of breakthrough overt HE recurrence was consistent for: sex, baseline Conn score, duration of current remission and diabetes. The differences in treatment effect could not be assessed in the following subpopulations due to small sample size: non-White (n=42), baseline MELD > 19 (n=26), Child-Pugh C (n=31), and those without concomitant lactulose use (n=26).

HE-related hospitalizations (hospitalizations directly resulting from HE, or hospitalizations complicated by HE) were reported for 19 of 140 subjects (14%) and 36 of 159 subjects (23%) in the XIFAXAN and placebo groups respectively. Comparison of Kaplan-Meier estimates of event-free curves showed XIFAXAN significantly reduced the risk of HE-related hospitalizations by 50% during the 6-month treatment period. Comparison of Kaplan-Meier estimates of event-free curves is shown in Figure 2.

Figure 2: Kaplan-Meier Event-Free Curves[1] in Pivotal HE Study (Time to First HE-Related Hospitalization in HE Study up to 6 Months of Treatment, Day 170) (ITT Population)



Note: Open diamonds and open triangles represent censored subjects.
[1] Event-free refers to non-occurrence of HE-related hospitalization.

15 REFERENCES

Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Sixth Edition, Wayne PA. *Approved Standard NCCLS Document M7-A6* January 2003; 23 (2).

16 HOW SUPPLIED/STORAGE AND HANDLING

The 200 mg tablet is a pink-colored, round, biconvex tablet with "Sx" debossed on one side. It is available in the following presentations:

- NDC 65649-301-03, bottles of 30 tablets
- NDC 65649-301-41, bottles of 100 tablets
- NDC 65649-301-05, carton of 100 tablets, Unit Dose

The 550 mg tablet is a pink-colored, oval, biconvex tablet with "rfx" debossed on one side. It is available in the following presentations:

- NDC 65649-303-02, bottles of 60 tablets
- NDC 65649-303-03, carton of 60 tablets, Unit Dose

Storage

Store XIFAXAN Tablets at 20–25°C (68–77°F); excursions permitted to 15–30°C (59-86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

17.1 Persistent Diarrhea

For those patients being treated for travelers' diarrhea, discontinue XIFAXAN if diarrhea persists more than 24-48 hours or worsens. Advise the patient to seek medical care for fever and/or blood in the stool [*see Warnings and Precautions (5.1)*].

17.2 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon which may lead to *C. difficile*. Patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If diarrhea occurs after therapy or does not improve or worsens during therapy, advise patients to contact a physician as soon as possible [*see Warnings and Precautions (5.4)*].

17.3 Administration with Food

Inform patients that XIFAXAN may be taken with or without food.

17.4 Antibacterial Resistance

Counsel patients that antibacterial drugs including XIFAXAN should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When XIFAXAN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by XIFAXAN or other antibacterial drugs in the future.

17.5 Severe Hepatic Impairment

Patients should be informed that in patients with severe hepatic impairment (Child-Pugh C) there is an increase in systemic exposure to XIFAXAN [*see Warnings and Precautions (5.4)*].

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