1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A randomized, double-blind, parallel group, placebo-controlled, multi-center, therapeutic equivalence study to compare Rifaximin 200 mg tablets (Sandoz GmbH) to Xifaxan® 200 mg tablets (Salix Pharmaceuticals, Inc.) and placebo in patients with travelers' diarrhea

Protocol No.:	1526 RIF_2 / NCT02920242
Test Product:	rifaximin
Indication:	Travelers' diarrhea
Development Phase:	Phase III
Sponsor:	Sandoz GmbH Biochemiestrasse 10 6250 Kundl Austria
Sponsor Representative Signatory:	[redacted]
Clinical Research Organization	[redacted]
Date of the Protocol:	October 29, 2015
Version of the Protocol:	2.0

Version History

Version	Date	Summary of Changes
Final Version 1.0	02 October 2015	--
Final Version 2.0	28 October 2015	Appendix II Visual Scale for Patient Assessment of Stools deleted; reference to most recent version of Declaration of Helsinki updated; text edits for clarification of dosing; formatting Changes made prior to submission to any regulatory agencies

2 SIGNATURE PAGES

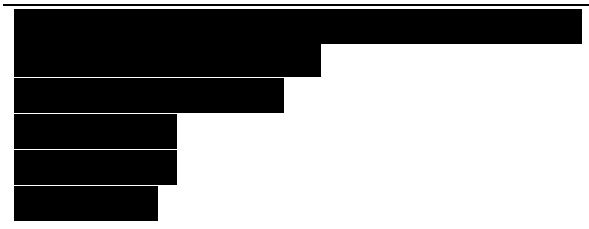
SPONSOR REPRESENTATIVE SIGNATURE PAGE

PROTOCOL TITLE: A randomized, double-blind, parallel group, placebo-controlled, multi-center, therapeutic equivalence study to compare Rifaximin 200 mg tablets (Sandoz GmbH) to Xifaxan® 200 mg tablets (Salix Pharmaceuticals, Inc.) and placebo in patients with travelers' diarrhea

PROTOCOL NUMBER: 1526 RIF_2

SPONSOR REPRESENTATIVE

Date (day/month/year)



Date (day/month/year)

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A randomized, double-blind, parallel group, placebo-controlled, multi-center, therapeutic equivalence study to compare Rifaximin 200 mg tablets (Sandoz GmbH) to Xifaxan® 200 mg tablets (Salix Pharmaceuticals, Inc.) and placebo in patients with travelers' diarrhea

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, the latest version of the Declaration of Helsinki, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

I understand that I may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate Ethics Committee, except when necessary to eliminate immediate hazards to the patient.

((Type name and job title))	Date (day/month/year)

(address)

(phone number)

CLINICAL RESEARCH ORGANIZATION SIGNATURE PAGE

PROTOCOL TITLE: A randomized, double-blind, parallel group, placebo-controlled, multi-center, therapeutic equivalence study to compare Rifaximin 200 mg tablets (Sandoz GmbH) to Xifaxan® 200 mg tablets (Salix Pharmaceuticals, Inc.) and placebo in patients with travelers' diarrhea

PROTOCOL NUMBER: 1526 RIF_2

[redacted]

[redacted]

Date (day/month/year)

[redacted]

Date (day/month/year)

[redacted]

Date (day/month/year)

3 GENERAL INFORMATION

PROTOCOL TITLE: A randomized, double-blind, parallel group, placebo-controlled, multi-center, therapeutic equivalence study to compare Rifaximin 200 mg tablets (Sandoz GmbH) to Xifaxan® 200 mg tablets (Salix Pharmaceuticals, Inc.) and placebo in patients with travelers' diarrhea

Protocol No.:	1526 RIF_2
Protocol Version and Date:	Version 2.0, October 29, 2015
Sponsor:	Sandoz GmbH Biochemiestrasse 10 6250 Kundl Austria
Clinical Research Organization:	[redacted]
Sponsor Signatory:	[redacted]
Central Laboratory:	[redacted]
Medical Monitor:	[redacted]

4 STUDY SYNOPSIS

Title of study:

A randomized, double-blind, parallel group, placebo-controlled, multi-center, therapeutic equivalence study to compare Rifaximin 200 mg tablets (Sandoz GmbH) to Xifaxan® 200 mg tablets (Salix Pharmaceuticals, Inc.) and placebo in patients with travelers' diarrhea

Sponsor: Sandoz GmbH

Study centers: It is planned that approximately 25 centers will be initiated in 3 countries.

Publications: None.

Planned Study Period:	**Development Phase:**
March 2016 to December 2017 (first patient first visit to last patient last visit)	Phase III

Objectives:

Primary objective:

To demonstrate the therapeutic equivalence of rifaximin 200 mg tablets to Xifaxan 200 mg tablets in patients with travelers' diarrhea (TD). In addition, the efficacy of rifaximin and Xifaxan will be compared to placebo to assess the assay sensitivity of the study.

Secondary objective:

To compare the safety and tolerability of rifaximin 200 mg tablets to Xifaxan 200 mg tablets and to placebo in patients with TD.

Methodology:

This is a randomized, double-blind, parallel group, placebo-controlled, multi-center, therapeutic equivalence study to compare rifaximin 200 mg tablets to Xifaxan and placebo. A total of 450 patients with TD will be randomized 2:2:1 (rifaximin:Xifaxan:placebo).

The study will consist of a Screening and Randomization Visit (informed consent, history, physical examination, vital signs, laboratory, randomization, and distribution of drug and diary); 1 dose of self-administered treatment with rifaximin, Xifaxan or placebo approximately once every 8 hours for 72 hours, for a total of 9 doses; phone call on Study Day 3; and a test of cure (TOC)/End of Study (EOS) visit at Study Day 5 (± 1 day). A follow-up phone call will be made on Study Day 30 (± 7 days) if there are any adverse events (AEs) ongoing at the time of the TOC/EOS Visit; any related AEs ongoing at the TOC/EOS Visit will be followed until resolution or until assessed by the Investigator to be permanent. Stool specimens for quantification and identification of enteric pathogens will be taken on Study Day 0 and Study Day 5 (± 1 day).

The Screening and Randomization procedures will be considered Study Day 0. The first administration of study drug will be immediately following randomization and will be considered Study Day 1; thus Study Day 0 will end and Study Day 1 will begin on the same calendar day. Subsequent days will be measured in 24 hour periods, not calendar days. Doses 1-3 of study drug will be self-administered on Study Day 1, doses 4-6 will be self-administered on Study Day 2 (beginning 24 hours after dose 1) and doses 7-9 will be self-administered on Study Day 3 (beginning 48 hours after dose 1); depending on the timing of the clinic visit on Study Day 0, the final doses taken on Study Day 3 may actually be taken on the 4th calendar day of the study.

Patients will be randomized (2:2:1) to receive rifaximin 200 mg tablets, Xifaxan 200 mg tablets or matching placebo. Patients will take a total of 9 doses of study drug.

The duration of participation for a patient is a maximum of 7 calendar days, including a maximum of 4 days of treatment with study drug (depending on the number of doses taken on Calendar Day 1).

Patients will maintain an electronic Patient Diary daily for recording the date, time and form (formed, soft, watery) of all stools passed; date and time of study drug administration; presence or absence and severity of signs and symptoms of enteric infection (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus); body temperature; and presence or absence of blood in

stool. Patients will document administration of concomitant medications and occurrence of any AEs on a paper Supplemental Form.

Number of patients:

A total of 450 patients will be enrolled into the study. Patients will be randomized in a 2:2:1 ratio such that 180 eligible patients will receive rifaximin 200 mg tablets, 180 eligible patients will receive Xifaxan 200 mg tablets and 90 eligible patients will receive placebo.

Diagnosis and main criteria for inclusion:

Inclusion criteria

Patients eligible for enrolment in the study must meet all of the following criteria:

1. Patient is able to read and understand the language of the Informed Consent Form and Patient Information
2. Patient has signed the Informed Consent Form
3. Adult male or female aged ≥ 18 years
4. International travelers (e.g., visiting students/faculty or international tourists) with a duration of stay in host country long enough to attend scheduled visits. [redacted]
5. Affected by naturally acquired acute diarrhea, defined as the passage of at least 3 unformed stools within the 24 hours immediately preceding randomization
6. At least one of the following signs and symptoms of enteric infection present at Screening:
    a. abdominal pain or cramps
    b. nausea
    c. vomiting
    d. fecal urgency
    e. excessive gas/flatulence
    f. tenesmus
7. Women of child-bearing potential (not post-menopausal or not surgically sterile) have a negative pregnancy test prior to beginning therapy and agree to use effective contraceptive methods during the study, as judged by the Investigator (including total abstinence from sexual intercourse)
8. Patient must have adequate general health as determined by the Investigator
9. Patient is willing and able (e.g., mental and physical condition) to participate in all aspects of the study, including providing an unformed stool sample at Screening and Randomization Visit, use of medication, completion of electronic Patient Dairy, attending scheduled visits, and compliance with protocol requirements as evidenced by providing signed written informed consent

    NOTE: the unformed stool provided at the Screening/Randomization Visit may be counted as 1 of the 3 unformed stools specified in Inclusion Criteria 5.

Exclusion criteria

Patients meeting any of the following criteria must not be enrolled in the study:

1. Hypersensitivity to rifaximin or any of the rifamycin antimicrobial agents or to any of the excipients of the study drug
2. Pregnant, breast feeding, or planning a pregnancy
3. Acute diarrhea for > 72 hours immediately prior to Randomization

4. Presence of:
    a. fever (≥ 100 °F/37.8 °C), or
    b. hematochezia (blood in stool; noted visually), or
    c. clinical findings suggesting moderate or severe dehydration
5. Active, uncontrolled, or clinically significant diseases or disorders of the heart, lung, kidney, gastrointestinal (GI) tract (other than infectious diarrhea in travelers), or central nervous system which would, in the judgment of the Investigator, compromise the patient's safety or successful participation in the clinical study
6. Administration of any of the following:
    a. any antimicrobial agents with an expected activity against enteric bacterial pathogens (e.g., trimethoprim/sulfamethoxazole, quinolones, azithromycin) within 7 days preceding randomization
    b. more than 2 doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents within 8 hours preceding randomization
7. Use of any drug such as aspirin or ibuprofen (Advil), which can cause GI bleeding

    NOTE: Acetaminophen (Tylenol) or paracetamol is acceptable for a maximum of 2 consecutive days.

    If required, antimalarial prophylactic treatment, including doxycycline, is permitted prior to and during the study
8. Presence of a medical condition with regular GI symptoms (e.g. Crohn's disease, ulcerative colitis, indeterminate colitis, previous bowel surgery which impacts absorption long term, thyrotoxicosis, short bowel syndrome, etc.)
9. Patient requires medication which alters GI function (e.g., prokinetic agents and other stimulants of GI contractility, laxatives and cathartics, antacids, or anti-diarrheal agents)
10. Patient requires use of long term antibiotics (e.g. urinary tract infection prophylaxis, acne, etc.)
11. Previous enrolment in trials involving rifaximin, previous enrolment in this study or participation in any other drug investigational trial prior to enrolment, within previous 6 months
12. Active alcohol/drug dependence or abuse (excluding tobacco abuse), as determined by the Investigator
13. Patient has an acute or chronic condition that, in the Investigator's opinion, would limit the patient's ability to complete or participate in this clinical trial
14. Patient is involved in the conduct and administration of this trial as an Investigator, sub-Investigator, study coordinator, or other study staff member, or the patient is a first degree family member, or significant other of any person involved in the conduct of this study.

Study drugs, dose and mode of administration:

Patients will receive rifaximin or Xifaxan 200 mg tablets, or matching placebo. Patients will receive 1 tablet of study drug approximately once every 8 hours for a total of 9 doses (3 tablets per day) starting immediately following the Screening and Randomization Visit on Study Day 0. Patients will participate in the study for a maximum of 7 calendar days.

Variables:

***Efficacy*:**

Primary endpoint

The primary endpoint is clinical cure at the TOC/EOS Visit (Study Day 5 ± 1 day). Clinical cure is defined as either:

- no stools or only formed stools within a 48 hour period and no fever, with or without other enteric symptoms, OR
- no watery stools or no more than two soft stools passed within a 24 hour period with no fever

and no other enteric symptoms except for mild excess gas/flatulence.

Secondary efficacy endpoints

- Time to Last Unformed Stool (TLUS) defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed
- proportion of patients with clinical failure defined as failure to achieve formed stool within ≤ 3 days (72 hours) of the start of treatment with the study drug or clinical deterioration or worsening of symptoms by Study Day 5
- Proportion of patients with improvement of diarrheal syndrome, defined as a reduction of ≥ 50% in the number of unformed stools (soft or watery) passed during intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug, compared to the number of unformed stools passed during the 24 hours immediately preceding first dose of study drug
- the number of unformed stools (soft or watery) passed during the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug
- the presence or absence and severity of signs and symptoms of enteric infection (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus) – the proportion of patients with signs and symptoms of enteric infection during the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug
- microbiological cure rate defined as a post-treatment culture that was negative for the pre-treatment etiologic pathogen.

Safety endpoints:

- Incidence of reported AEs
- Changes in vital signs and clinical laboratory parameters.

Pharmacokinetics: There is no pharmacokinetic evaluation planned in this study.

Statistical Methods:

Sample size and power:

A sample size of 135 in the generic rifaximin and 135 in the reference listed drug (RLD) Xifaxan treatment groups achieve approximately [redacted] power to detect therapeutic equivalence when the margin of equivalence, given in terms of the difference, extends from -0.20 to 0.20.

Concerning the assessment of study sensitivity, a sample size of 170 in the generic rifaximin group and RLD Xifaxan® group and 85 in the placebo group achieve approximately [redacted] power to detect a difference between the group proportions of [redacted]

Patients will be randomized 2:2:1 to generic rifaximin (n=180), Xifaxan (n=180), and placebo (n=90). A total of 450 patients will be randomized. As it can be anticipated that no more than 5% of patients will be excluded from the modified Intent to Treat (mITT) population, and no more than 20% of patients from the mITT population will be excluded from the PP population this sample size will have sufficient power to show therapeutic equivalence and study sensitivity.

Efficacy:

The primary endpoint will be clinical cure at the TOC/EOS Visit (Study Day 5 ± 1 day). Equivalence will be concluded if the 90% confidence interval of the difference of the success proportions between rifaximin and Xifaxan is completely contained within the interval [-0.20; 0.20]. Two, one-sided Z tests at the 5% significance level will be used. The PP population will be the primary analysis set.

Study sensitivity will be evaluated by comparing the success proportions between rifaximin and placebo and Xifaxan and placebo. The two-sided Z test with pooled variance will be used. The significance level of the test is 0.05. The mITT population will be the primary analysis set.

The primary endpoint will also be analyzed by subgroups according to the pathogen status at baseline.

Secondary efficacy variables

The analysis of all secondary endpoints will be performed in the mITT and PP populations.

TLUS will be compared between the three treatment groups using a Cox proportional hazards model. The proportion of patients with clinical failure, with improvement in diarrheal syndrome and with signs and symptoms of enteric infection will be compared between the three treatment groups with two-sided Z tests. The significance level of these tests will be set to 0.05. For patients with a positive pre-treatment culture, the proportion of patients with microbiological cure will be compared between the three treatment groups with two-sided Z tests. The significance level of these tests will be set to 0.05. The number of unformed stools passed per unit time will be analyzed using repeated measures Poisson regression.

Safety:

All patients who are treated with any amount of study drug will be evaluated for safety. Adverse events will be summarized by the number and percentage of patients experiencing events by system organ class, preferred term and severity. Changes in vital signs and clinical laboratory measurements will be summarized descriptively by assessment time-points. Other safety variables will be summarized and listed.

Version and date of the protocol synopsis: 2.0**,** October 29, 2015

5 TABLE OF CONTENTS

5.1 List of Tables

5.2 List of Figures

5.3 List of Appendices and Supplements

6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ADR	adverse drug reaction
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CRO	Clinical Research Organization
CSR	clinical study report
EAEC	enteroaggregative *E.coli*
EC	Ethics Committee
E.coli	*Escherichia coli*
eCRF	electronic Case Report Form
EOS	end of study
ETEC	enterotoxigenic *E.coli*
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IWRS	Interactive Web Response System
LOCF	last observation carried forward
LPPV	Local Qualified Person for Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat (Population)
OGD	(FDA's) Office of Generic Drugs
PP	Per Protocol (Population)
RLD	reference listed drug
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
TD	travelers' diarrhea
TLUS	time to last unformed stool
TOC	test of cure
USA	United States of America
WHO	World Health Organization

7 INTRODUCTION

7.1 Background

7.1.1 Disease epidemiology

Travelers' diarrhea (TD) may be experienced by >60% of travelers from developed countries who visit developing countries, accounting for 40,000 travelers daily or > 15 million travelers annually[1]. Travelers' diarrhea is usually contracted from contaminated food or water. Bacteria, in particular enterotoxigenic *Escherichia coli* (ETEC), are the most common cause of TD. Other bacteria implicated in travelers' diarrhea include enteroaggregative *E.coli* (EAEC), *Shigella, Salmonella*, and *Campylobacter*. Viruses (including Rotavirus) and protozoa (*Giardia lamblia*), make up the remainder of known causes[2,3,4].

The average duration of untreated travelers' diarrhea is approximately 4 days, with 50% of patients being free of symptoms within 48 hours[5,6]. In a study of 1,455 Austrian tourists, abdominal cramps were reported in just over half of all patients, less than one third of patients reported nausea and/or vomiting and 13% of patients reported fever[6]. Travelers' diarrhea tends to have a longer duration in patients with other symptoms in addition to diarrhea (suggestive of severe travelers' diarrhea) and patients in whom pathogens are identified[7].

7.1.2 Rifaximin Mechanism of Action

The reference listed drug (RLD) in this study is the rifaximin 200 mg tablet marketed in United States of America (USA) by Salix Pharmaceuticals, Inc. under the trade name Xifaxan®. The investigational product produced by Sandoz GmbH also contains 200 mg of rifaximin.

Rifaximin is a non-aminoglycoside semi-synthetic, non-systemic antibacterial drug derived from rifamycin SV, a structural analog of rifampin. Rifaximin acts by binding to the beta-subunit of bacterial deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase, resulting in inhibition of bacterial RNA synthesis, consequently inhibiting the growth of bacteria.

Rifaximin is approved in a number of countries (including the USA) for the treatment of TD.

Rifaximin has been shown to be active against *E.coli* (enterotoxigenic and enteroaggregative strains) in both *in vitro* and clinical studies of infectious diarrhea[8].

Additional information regarding indications and usage, contraindications, warnings and precautions, and adverse reactions is provided in the prescribing information for rifaximin[9].

7.1.2.1 Pre-clinical Data

Teratogenic effects (ocular, oral and maxillofacial, cardiac, and lumbar spine malformations) were observed in animal reproduction studies following administration of rifaximin to pregnant rats and rabbits during organogenesis at doses approximately 0.9 to 5 times and 0.7 to 33 times, respectively of the recommended human doses of 600 mg to 1650 mg per day.

7.1.2.2 Pharmacokinetic Data

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).

A high-fat meal consumed 30 minutes prior to rifaximin dosing in healthy subjects delayed the mean time to peak plasma concentration from 0.75 to 1.5 hours and increased the systemic exposure (area under the curve, AUC) of rifaximin by 2-fold but did not significantly affect the maximum concentration (C_{max}).

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 rifaximin was administered.

In an *in vitro* study, rifaximin was metabolized mainly by CYP3A4. Rifaximin accounted for 18% of radioactivity in plasma.

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 mostly as the unchanged drug; 0.32% was recovered in urine mostly as metabolites with 0.03% as the unchanged drug.

This suggests that the absorbed rifaximin undergoes metabolism with minimal renal excretion of the unchanged drug.

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

7.1.3 Alternative Treatments

Alternatives to treatment with rifaximin include other antibiotics (e.g., ciprofloxacin, levofloxacin, azithromycin), or a combination of an anti-motility agent (e.g., loperamide) with an antibiotic. Adequate fluid intake with oral rehydration solutions are recommended, or foods which are relatively high in salt, such as crackers.

7.2 Rationale

The rifaximin 200 mg tablet is currently approved in the USA for the treatment of travelers' diarrhea caused by noninvasive strains of *E.coli* in adults and pediatric patients 12 years of age and older. This study is being carried out to demonstrate the therapeutic equivalence of rifaximin to the Xifaxan in patients with TD. [redacted]

Rifaximin is recommended for the treatment of diarrhea caused by bacteria, and is noted to be effective at treating diarrhea caused by *E.coli*. [redacted] Because appropriate treatment should be introduced as soon as possible, it is not

necessary to have laboratory confirmation of the presence of intestinal *E.coli* in the stool, prior to initiating treatment, since strong suspicion exists that infection is caused by rifaximin susceptible *E.coli*[10].

This study will be conducted in compliance with the protocol and with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP).

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- to demonstrate the therapeutic equivalence of rifaximin 200 mg tablets to Xifaxan 200 mg tablets in patients with TD.

In addition, the efficacy of rifaximin and Xifaxan will be compared to placebo to assess the assay sensitivity of the study.

8.2 Secondary Objective

The secondary objective of this study is:

- to compare the safety and tolerability of rifaximin 200 mg tablets to Xifaxan 200 mg tablets and to placebo in patients with TD.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a randomized, double-blind, parallel group, placebo-controlled, multi-center therapeutic equivalence study to compare rifaximin 200 mg tablets to Xifaxan 200 mg tablets and placebo in patients with TD.

The study design is summarized in Figure 9–1; Table 9-1 presents the Schedule of Events.

Patients will undergo screening procedures at the study site and eligible patients will be randomized to treatment. The first dose will be self-administered immediately following randomization, thus initiating Study Day 1. Subsequent doses will be taken approximately once every 8 hours for 72 hours for a total of 9 doses. Study Day 1 will begin with the first administration of study drug and Study Day 2 will begin 24 hours after the first treatment. Study Day 3 will begin 48 hours after the first treatment. Depending on the timing of the first administration of study drug on Visit 1, a Study Day may extend across 2 calendar days. Thus, the final dose(s) of study drug taken on Study Day 3 may actually be taken on the 4th calendar day of the study.

Treatments administered (randomized in a ratio of 2:2:1) will be:

- rifaximin 200 mg tablets
- Xifaxan 200 mg tablets
- placebo tablets

Patients will be contacted by telephone on Study Day 3 to determine if their condition has improved. Patients will return to the study site on Study Day 5 (± 1 day) for the test of cure (TOC)/End of Study (EOS) visit. Patients will participate in the study for a maximum of 7 calendar days.

Patients will maintain an electronic Patient Diary daily for recording the date, time and form (formed [retains shape], soft [assumes shape of container], watery [can be poured]) of all stools passed; the time and date of study drug administration; the presence or absence and severity of signs and symptoms of enteric infection (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus); body temperature; and presence or absence of blood in the stool. The use of any concomitant medications and the occurrence of any AEs will be recorded on a paper Supplemental Form. Stool specimens for quantification and identification of enteric pathogens will be taken at Screening (Study Day 0) and Study Day 5. Clinical laboratory tests (hematology, chemistry and urinalysis), assessment of vital signs and physical examinations will be carried out at Screening (Study Day 0) and Study Day 5.

Stool, blood and urine samples will be analyzed at a central laboratory; study treatment retention samples will be stored in national depots (Section 18.4.2). A separate laboratory

manual will provide details for sampling handling, storage and shipping of all biological samples.

The primary efficacy endpoint is clinical cure at the TOC/EOS Visit, with clinical cure defined as either:

- no stools or only formed stools within a 48 hour period and no fever, with or without other enteric symptoms, OR
- no watery stools or no more than two soft stools passed within a 24 hour period with no fever and no other enteric symptoms except for mild excess gas/flatulence.

Secondary efficacy endpoints are:

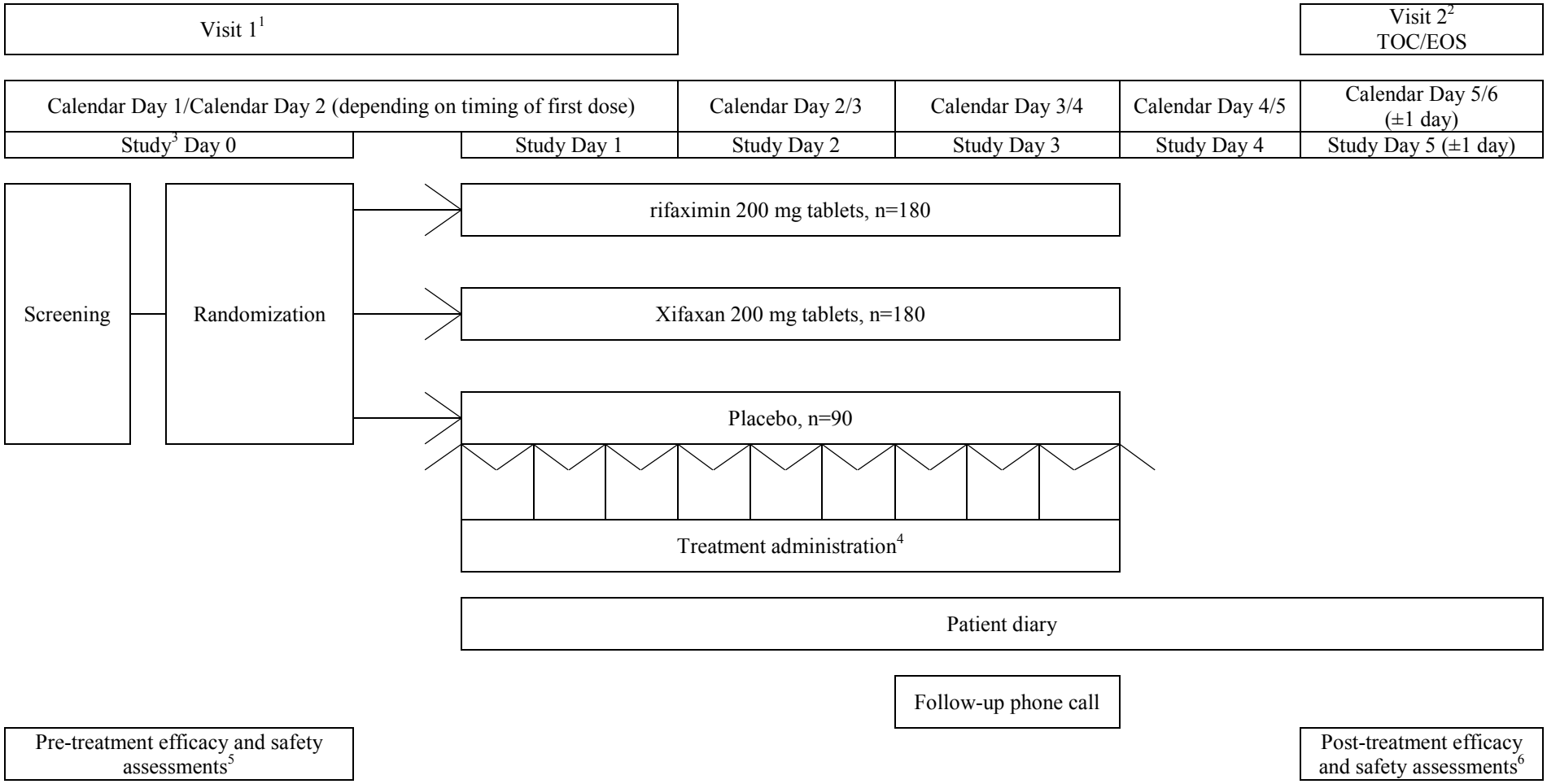
- time to last unformed stool (TLUS)
- proportion of patients with clinical failure
- proportion of patients with improvement of diarrheal syndrome
- number of unformed stools (soft or watery) passed during the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug
- presence or absence and severity of signs and symptoms of enteric infection (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus)
- microbiological cure rate.

Definitions of these endpoints are given in Section 11.1.2.

Safety endpoints are the incidence of reported AEs and changes in vital signs and clinical laboratory parameters.

There is no pharmacokinetic evaluation planned in this study.

Figure 9–1 Study Design – Flow Chart



AE=adverse event; EOS=end of study; TOC=test of cure

1. At Visit 1 (Study Day 0) patients will undergo screening and randomization and then eligible patients will self-administer their first tablet (initiating Study Day 1).
2. Depending on the timing of the first dose, and given the window of ± 1 day for the TOC/EOS Visit, the TOC/EOS Visit can take place anywhere from Calendar Day 4 to Calendar Day 7.
3. Study Days are measured in 24 hour periods, starting with the first dose of study drug. Depending on the timing of the first dose, 1 Study Day may extend across 2 calendar days.
4. One tablet of the randomized treatment approximately every 8 hours, for a total dose of 9 tablets.
5. Stool sample for diagnosis and culture; pre-enrollment stool form and frequency; physical examination; vital signs; clinical laboratory tests; urine pregnancy test (if appropriate); distribution and instructions on use of thermometer, electronic Patient Diary and paper Supplemental Form for documentation of concomitant medications and AEs.
6. Stool sample for diagnosis and culture; physical examination; vital signs; clinical laboratory tests; urine pregnancy test (if appropriate); AE and concomitant medication assessment. Collection of Patient Diary.

Table 9-1 Schedule of Events

Procedure	Study Day 0* Screening/ Randomization	Study Day 1*	Study Day 2	Study Day 3	Study Day 4	Study Day 5* (± 1 day) TOC/EOS	Day 30 (± 7 days) Follow-up Phone Call
Informed Consent[1]	X						
Eligibility Verification	X						
Medical History, Demographics	X						
Physical Examination[2]	X					X	
Vital Signs[3]	X					X	
Clinical Laboratory Tests[4]	X					X	
Signs and Symptom Assessment of TD	X					X	
Stool Culture/Fecal Leukocytes[5]	X					X	
Urine Pregnancy Test[6]	X					X	
Randomization, Study Drug Dispensing	X						
Study Drug Administration[7]		X	X	X			
Completion of Electronic Patient Diary[8]		X	X	X	X	X	
Telephone Call to Patient				X[9]			
Concomitant Medication Use[10]	X	X	X	X	X	X	
Adverse Event Assessment[10]	X	X	X	X	X	X	X[11]
Review of Diary/Supplemental Form				X		X	
Drug Accountability and Compliance						X	

AE=Adverse Event; EOS=End of Study; ICF=Informed Consent Form; TD=travelers' diarrhea; TOC=test of cure

* Screening/Randomization (Study Day 0) and Study Day 1 are the same day. Study days are 24 hour periods. Study Day 1 will begin with the administration of the first dose of study drug, Study Day 2 will begin 24 hours after the administration of the first dose of study drug, and so on. Depending on the timing of the first dose of study drug, one Study Day may extend over two calendar days. Depending on the timing of the first dose, and given the window of ± 1 day for the TOC/EOS Visit, the TOC/EOS Visit can take place anywhere from Calendar Day 4 to Calendar Day 7.

1 Informed consent must be obtained before the patient undergoes any study-specific procedures. The Investigator must confirm that the patient is able to read and understand the language of the ICF, Patient Information, the electronic Patient Diary, and the Supplemental Form.

2 Weight and height will be measured at Screening; weight will be measured at the TOC/EOS visit. Body mass index (BMI) will be calculated at Screening and TOC/EOS.

3 Vital signs (respiratory rate, heart rate, blood pressure, and body temperature) will be performed at Screening and the TOC/EOS Visit. They will be obtained in the sitting position after the patient has rested for 5 minutes. The date and time of the assessment should be recorded.

4 To include hematology, clinical chemistry and urinalysis.

5 A stool sample will be obtained for fecal leukocyte testing and culture prior to randomization to study drug and on TOC/EOS. Stool culture for pathogenic organisms including: Enterotoxigenic *Escherichia coli* (ETEC); Enteroaggregative *E.coli* (EAEC); *Shigella* spp; *Salmonella* spp; *Campylobacter jejuni; Plesiomonas* spp; *Aeromonas* spp; Rotavirus; *Giardia lamblia; Entamoeba histolytica, Cryptosporidium* spp.

6 For female patients of childbearing potential (not post-menopausal or have not undergone surgical sterilization), the results of the urine pregnancy test must be negative to confirm eligibility prior to randomization.
7 The first dose of study drug is considered to be on Day 1, and is to be taken as soon as possible following completion of the Screening/Randomization procedures. The remaining 8 doses are to be taken at even intervals for 3 doses per day – a total of 9 doses of study drug are to be taken.
8 At Screening/Randomization, the patient will be given an electronic Patient Diary in which to record his/her symptoms; time of study drug administration; and date, time and form of all stools passed. The Patient Diary will be reviewed by the Investigator during the call on Study Day 3 at the TOC/EOS Visit.
9 Site will contact patient on Study Day 3 to check on their clinical status (i.e., if their condition has improved) and review completion of Diary and Supplemental Form. Information on AEs and concomitant medication will also be collected.
10 Patients will be given a paper Supplemental Form for documentation of the administration of any concomitant medications or the occurrence of any AEs. The Form will be reviewed by the Investigator during the call on Study Day 3 and at the TOC/EOS Visit.
11 A follow-up phone call is to be performed should the patient have any ongoing AE at the TOC/EOS Visit. Any ongoing related AEs will be followed until resolution or until assessed by the Investigator to be permanent.

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9.1.2 Study Assessments

Investigators will document data from all study assessments at each visit in the electronic Case Report Form (eCRF). Patients will complete their Patient Diary daily, and their Supplemental Form as required, from the time of first administration of study drug until they return to the study facility for the TOC/EOS Visit.

9.1.2.1 Screening and Randomization Visit (Study Day 0)

Screening procedures are as follows:

- ensure the patient is able to read and understand the Informed Consent Form (ICF) documents, and complete the Patient Diary and Supplemental Form
- obtain signed and dated informed consent
- check eligibility against study Inclusion and Exclusion Criteria (Sections 9.3.1 and 9.3.2, respectively)
- record medical and surgical history
- record demographic information (age, race, ethnicity and gender; country of residence; date of arrival in host country; previous country[s] visited between residence and host country)
- physical examination, including weight, height, and body mass index (BMI) (Section 12.2)
- vital signs (body temperature; respiratory rate, heart rate, blood pressure in the sitting position after 5 minutes rest; Section 12.3)
- clinical laboratory tests (hematology, chemistry, urinalysis; Section 12.4)
- signs/symptoms of TD (Section 11.2.1)
- baseline stool data (number and form of stools in the previous 24 hours; Section 11.2.2)
- stool sample (unformed) to be used for diagnosis and culture (Section 11.2.3); this stool sample may count as 1 of the 3 unformed stools that must be passed in the 24 hours prior to Randomization, as specified by the Inclusion Criteria
- urine pregnancy test for females of childbearing potential (not post-menopausal or who have not undergone surgical sterilization), only
- provide patients with Patient Diary to be completed during the study; patients will also receive instructions and practice in how to use Diary
- provide patients with the (paper) Supplemental Form to document the administration of any concomitant medications or occurrence of any AEs
- record prior medication taken within previous 4 weeks and occurrence of any AE (Section 12)
- dispense thermometer for patient use, with instructions for use
- documentation of any pre-treatment AEs

Once all Screening procedures are complete, eligible patients will be randomized to treatment (rifaximin, Xifaxan, or placebo) and receive assigned study treatment.

9.1.2.2 Study Day 1 (Initiation of Study Treatment)

Randomized patients will self-administer their first dose of the study drug, initiating Study Day 1. The time of this dose will be recorded in the Patient Diary. After this, patients can leave the study site.

Study days are measured in 24 hour periods, not calendar days. Because doses of study drug are to be taken approximately once every 8 hours, a study day may extend over 2 calendar days. Thus, depending on how many tablets were taken on Study Day 1, the final doses of study drug taken on Study Day 3 may be taken on the 4th calendar day of the study.

From the time of the first study drug administration, patients will be asked to record the following in the Patient Diary:

- date, time and form (formed, soft, watery) of all stools passed
- date and time of study drug administration
- presence or absence and severity of enteric symptoms (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus)
- presence or absence of any blood in stool
- body temperature.

Patients will document the administration of any concomitant medication and occurrence of any AEs on the (paper) Supplemental Form.

9.1.2.3 Study Day 2

Study Day 2 will begin 24 hours after the administration of the first dose of study treatment. On Study Day 2, patients will:

- take the next 3 doses of their randomized study treatment, 1 tablet every 8 hours
- complete the Patient Diary, recording:
  - date, time and form of all stools passed
  - date and time of study drug administration
  - the presence or absence and severity of enteric symptoms (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus)
  - presence or absence of any blood in stool
  - body temperature.

Patients will document the administration of any concomitant medication or occurrence of any AEs on the Supplemental Form.

9.1.2.4 Study Day 3

Study Day 3 will begin 48 hours after the administration of the first dose of study treatment. On Study Day 3, patients will:

- take final 3 doses of study drug, 1 tablet every 8 hours
- document the administration of any concomitant medication and occurrence of any AEs on the (paper) Supplemental Form
- complete the Patient Diary, recording:

  - date, time and form of all stools passed
  - date and time of study drug administration
  - the presence or absence and severity of enteric symptoms (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus)
  - presence or absence of any blood in stool
  - body temperature.
- receive a telephone call from the study site to allow the site to:
  - determine if the patient's condition has improved.
  - confirm if the patient has noted the presence of any blood in the stool, as possibly indicative of infection with pathogens other than *E.coli*
  - confirm that patients are documenting any concomitant medications and AEs on the paper Supplement Form
  - record any concomitant medications noted in the Supplemental Form
  - record any AEs noted on the Supplemental Form
  - confirm that patients have completed the Patient Diary to date, and review Diary entries.

If a patient's condition has worsened, or if a patient has noted blood in the stool, the patient may be requested to return to the study facility. If in the opinion of the Investigator the patient requires alternate or supplemental therapy, the patient should be discontinued (Section 9.3.3), and provided with effective treatment.

9.1.2.5 Study Day 4

Study Day 4 will begin 72 hours after the administration of the first dose of study treatment. On Study Day 4, patients will complete the Patient Diary, recording:

- date, time and form of all stools passed
- the presence or absence and severity of enteric symptoms (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus)
- presence or absence of any blood in stool
- body temperature.

Patients will document the administration of any concomitant medication or occurrence of any AEs on the (paper) Supplemental Form.

There should be no patient administration of study drug on Study Day 4. If however, study drug is administered the time and date of administration should be recorded in the Patient Diary. Any study administered as of Study Day 4 would be considered a protocol violation.

9.1.2.6 Study Day 5 (± 1 day), Test of Cure/End of Study Visit

Depending on the timing of the first administration of the study drug, the TOC/EOS Visit may take place anywhere from Calendar Day 4 to Calendar Day 7.

Patients will complete the final entries of the Patient Diary, recording:

- date, time and form of all stools passed
- the presence or absence and severity of enteric symptoms (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus)
- any blood in stool
- body temperature.

Patients will document the administration of any concomitant medication or occurrence of any AEs on the (paper) Supplemental Form.

Patients will also return to the study site on Study Day 5 for the TOC/EOS Visit. The following will be performed/documented:

- physical examination, including weight and calculation of BMI
- vital signs
- clinical laboratory tests
- signs/symptoms of TD
- stool sample for culture
- urine pregnancy test, if applicable
- Investigator review of Patient Diary to ensure entries are complete
- concomitant medications noted by the patient in the Supplemental Form
- AEs noted by the patient on the Supplemental Form
- drug accountability and patient compliance check.

Once the above procedures have been carried out, patients will be considered to have completed the study. Patients with ongoing AEs on Day 5 will be followed up with a phone call on Day 30 (± 7 days); any related AE ongoing on Day 5 will be followed until the AE has resolved or until it is judged by the Investigator to be permanent (Section 12.1.4).

9.2 Discussion of Study Design

The study was designed following the guidance published by the Food and Drug Administration's (FDA) Office of Generic Drugs (OGD)[11]. The guidance requires a randomized, double blind, parallel, placebo controlled study in male and non-pregnant female patients with TD to demonstrate the therapeutic equivalence of rifaximin 200 mg tablets to Xifaxan 200 mg tablets. All the main design features of the study are in accordance with the OGD guidance (e.g. study population, efficacy endpoints, the controls used [Xifaxan and placebo] and statistical methodology).

The equivalence margin for the primary endpoint was recommended by the OGD guidance (the 90% confidence interval [CI] of the test - reference difference between products for the primary endpoint has to be contained within [-0.20, +0.20] using the per protocol [PP] population). A placebo control arm was included to demonstrate that rifaximin and Xifaxan are active, and to establish that the study is sufficiently sensitive to detect differences between products.

9.2.1 Risk/Benefit and Ethical Assessment

Rifaximin is already approved by the FDA for use in the treatment of TD at the posology used in the present study.

The risks associated with the treatment are well established and considered acceptable (see Xifaxan full prescribing information in Appendix I). In two placebo controlled trials comparing Xifaxan 200 mg three times daily (n=320) with placebo (n=228), discontinuations due to adverse reactions occurred in only 0.4% of patients (events of taste loss, dysentery, weight decrease, anorexia, nausea and nasal passage irritation). Of the adverse reactions that occurred at a frequency >2% in Xifaxan-treated patients, headache was the only event which occurred at a higher rate with Xifaxan (10%) than placebo (9%).

As TD normally spontaneously resolves without treatments after approximately 4 days[5], including a placebo arm (as recommended by the OGD) is considered to be ethically acceptable. The 2:2:1 randomization ensures that the maximum number of patients receive active treatment. In addition, patients will receive a phone call on Study Day 3 to identify patients who may need to receive an alternative or supplemental therapy.

There are no adequate and well-controlled studies in pregnant women, however pregnant or lactating women will not be enrolled in this study. There is no information regarding the presence of rifaximin in human milk, the effects of rifaximin on the breastfed infant, or the effects of rifaximin on milk production. Any pregnancy that occurs during the study must be handled as described in Section 12.1.6.

The safety and effectiveness of rifaximin has not been established in pediatric patients less than 12 years of age with TD. Patients less than 18 years of age will not be enrolled in this study.

Because this study will enroll tourists who will not be local to the study facility, the Investigator will ensure that the prospective patient is able to understand the language of the study (Section 17.3) and is able to understand instructions for, and adequately complete, specified study activities (Section 18.2), prior to enrollment in the study.

9.2.2 Early Termination

This study may be terminated at any time by the Sponsor to ensure patients' safety, if the Investigator does not adhere to the protocol or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study. In this event, the Sponsor will inform the study Investigators, institutions and all regulatory authorities.

If, in the opinion of the Investigator, the clinical observations in the study suggest that it might not be justifiable for medical reasons to continue, he/she may terminate the study after consultation with the Sponsor. Reasons for discontinuation have to be documented appropriately and to be provided to the Sponsor and the Ethics Committee (EC).

In case of premature discontinuation of the study a complete final examination must be performed for each patient as far as possible with regard to the patient's health conditions and as far as necessary with regard to safety aspects and the validity of study results.

9.2.3 End of Study

The end of study will be at the time of last patient, last visit.

When the last patient has completed the study, the remaining issues with eCRFs, study treatments, other study materials delivered to the study center, as well as archiving of study documents by the Investigator, will be dealt with.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Patients eligible for enrolment in the study must meet all of the following criteria:

1. Patient is able to read and understand the language of the ICF and Patient Information
2. Patient has signed the ICF
3. Adult male or female aged ≥ 18 years
4. International travelers (e.g., visiting students/faculty or international tourists) with a duration of stay in host country long enough to attend scheduled visits. [redacted]
5. Affected by naturally acquired acute diarrhea, defined as the passage of at least 3 unformed stools within the 24 hours immediately preceding randomization
6. At least one of the following signs and symptoms of enteric infection present at Screening:
    a. abdominal pain or cramps
    b. nausea
    c. vomiting
    d. fecal urgency
    e. excessive gas/flatulence
    f. tenesmus
7. Women of child-bearing potential (not post-menopausal or not surgically sterile) have a negative pregnancy test prior to beginning therapy and agree to use effective contraceptive methods during the study, as judged by the Investigator (including total abstinence from sexual intercourse)
8. Patient must have adequate general health as determined by the Investigator
9. Patient is willing and able (e.g., mental and physical condition) to participate in all aspects of the study, including providing an unformed stool sample at Screening and Randomization Visit, use of medication, completion of electronic Patient Dairy, attending scheduled visits, and compliance with protocol requirements as evidenced by providing signed written informed consent

NOTE: the unformed stool provided at the Screening/Randomization Visit may be counted as 1 of the 3 unformed stools specified in Inclusion Criteria 5.

9.3.2 Exclusion Criteria

Patients meeting any of the following criteria must not be enrolled in the study:

1. Hypersensitivity to rifaximin or any of the rifamycin antimicrobial agents or to any of the excipients of the study drug
2. Pregnant, breast feeding, or planning a pregnancy
3. Acute diarrhea for > 72 hours immediately prior to Randomization
4. Presence of:
    a. fever (≥ 100 °F/37.8 °C), or
    b. hematochezia (blood in stool; noted visually), or
    c. clinical findings suggesting moderate or severe dehydration
5. Active, uncontrolled, or clinically significant diseases or disorders of the heart, lung, kidney, GI tract (other than infectious diarrhea in travelers), or central nervous system which would, in the judgment of the Investigator, compromise the patient's safety or successful participation in the clinical study
6. Administration of any of the following:
    a. any antimicrobial agents with an expected activity against enteric bacterial pathogens (e.g., trimethoprim/sulfamethoxazole, quinolones, azithromycin) within 7 days preceding randomization
    b. more than 2 doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents within 8 hours preceding randomization
7. Use of any drug such as aspirin or ibuprofen (Advil), which can cause GI bleeding

    NOTE: Acetaminophen (Tylenol) or paracetamol is acceptable for a maximum of 2 consecutive days.

    If required, antimalarial prophylactic treatment, including doxycycline, is permitted prior to and during the study
8. Presence of a medical condition with regular GI symptoms (e.g. Crohn's disease, ulcerative colitis, indeterminate colitis, previous bowel surgery which impacts absorption long term, thyrotoxicosis, short bowel syndrome, etc.)
9. Patient requires medication which alters GI function (e.g., prokinetic agents and other stimulants of GI contractility, laxatives and cathartics, antacids, or anti-diarrheal agents)
10. Patient requires use of long term antibiotics (e.g. urinary tract infection prophylaxis, acne, etc.)
11. Previous enrolment in trials involving rifaximin, previous enrolment in this study or participation in any other drug investigational trial prior to enrolment, within previous 6 months
12. Active alcohol/drug dependence or abuse (excluding tobacco abuse), as determined by the Investigator

13. Patient has an acute or chronic condition that, in the Investigator's opinion, would limit the patient's ability to complete or participate in this clinical trial
14. Patient is involved in the conduct and administration of this trial as an Investigator, sub-Investigator, study coordinator, or other study staff member, or the patient is a first degree family member, or significant other of any person involved in the conduct of this study.

9.3.3 Withdrawal of Patients

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, non-compliance or other administrative reasons.

Patients whose condition worsens and in the opinion of the Investigator require alternate or supplemental therapy for the treatment of TD should be discontinued, and provided with effective treatment. A patient may also be removed, if necessary, to protect their health or the integrity of the study. This determination will be made by the Principal Investigator/Sub-Investigator. Every attempt will be made to record reasons for withdrawal.

Patients whose participation in the study is discontinued (for any reason) will not be replaced.

If a patient's participation is terminated prematurely, the cause for the early termination and the date and time of the termination will be documented in the eCRF, on the source documents and in the final clinical study report (CSR).

If a patient withdraws or is dismissed from the study, every effort will be made to see the patient and all procedures planned for the TOC/EOS Visit will be completed, where possible.

10 TREATMENT OF PATIENTS

10.1 Identity of Study Treatments

Details of the study treatments are presented in Table 10-1.

Table 10-1 Study Treatments

Drug Name	Rifaximin	Xifaxan	Placebo
Active ingredient	rifaximin	rifaximin	None
Strength	200 mg	200 mg	Not applicable
[redacted]	[redacted]	[redacted]	[redacted]
Dosage Form	Tablet		
Route of administration	Oral		
Mode of administration	With or without food, to be taken with a glass of water		
Dose	1 × 200 mg 3 times per day (approximately every 8 hours, daily dose of 600 mg) for 72 hours		1 tablet 3 times per day (approximately every 8 hours) for 72 hours
Manufactured by/for:	[redacted]	Salix Pharmaceuticals, Inc.	[redacted]

All tablets will be visually the same to ensure that all persons involved in the study remain blinded to treatment.

10.1.1 Administration of Study Treatments

Patients will be randomized (2:2:1) to receive rifaximin 200 mg tablets, Xifaxan 200 mg tablets or matching placebo tablets. Treatment will be self-administered by the patients with a glass of water. The first study treatment will be taken at the study site, immediately following c randomization. Subsequent doses should be taken once approximately every 8 hours, for a total of 9 doses.

Study drug can be taken with or without food.

10.1.2 Missed Doses

Missed doses should be taken as soon as possible, and all subsequent doses should be taken at their regular time.

10.2 Study Treatment Packaging and Labelling

The packaging and labelling of all 3 study drugs (rifaximin, Xifaxan, and placebo) will be the same to ensure that all persons involved in the study remain blinded to treatment.

10.2.1 Packaging

All study tablets will be packaged in bottles. Each bottle will contain 12 tablets, which includes 3 extra tablets to allow for loss of a tablet.

Patients will be instructed to take only 9 tablets (1 tablet approximately every 8 hours for 72 hours).

10.2.2 Labelling

Bottles will be labeled to clearly identify that the contents are for investigational use only, and with appropriate study details, including storage instructions.

10.2.3 Storage

Tablets should be stored on site and by the patient at room temperature not above 25°C/77°F, in a dry location.

10.2.4 Blinding and Randomization of Study Treatments

At each study center, patients who are eligible to enter the double-blind treatment period will be randomized to generic rifaximin 200 mg, Xifaxan 200 mg or matching placebo according to a 2:2:1 randomization ratio through an Interactive Web Response System (IWRS). Prior to randomization via IWRS, the IWRS will send an initial shipment that confirms sufficient inventory to treat each randomized patient.

The staff at the study center, the Sponsor and its representatives, and all patients will be blinded to the identity of the investigational product. The study blinding may only be broken for an individual patient in the case of an emergency and when the knowledge of the investigational product is essential for the clinical management of the safety of this patient as described in Section 10.3.

10.3 Procedure for Breaking the Randomization Code

The treatment code may be broken for an individual patient in the case of an emergency and when the knowledge of the investigational product is essential for the clinical management of the safety of this patient. The Investigator must make every effort to contact the Medical Monitor before breaking the treatment code. The Investigator will be able to access the IWRS database to receive the treatment code, 24 hours a day and 7 days a week. A record will be kept at each study center of all broken treatment codes, of the person who broke the treatment code, date, time and of the reasons for breaking the treatment code. This will also be

documented in the eCRF. The treatment code must not be recorded on the patient's eCRF. In the case of a code break, the Investigator must inform the Sponsor or its representative immediately, without revealing to the Sponsor or its representative personnel the result of the code break.

The Sponsor will have a designated Safety Manager at the Central Case Processing Site that has access to the randomization codes via the IWRS who may unblind a case if it is deemed medically appropriate.

10.4 Patient Compliance

Patients will enter the time and date of each treatment administration in the Patient Diary. This information will be reviewed by the Investigator at the TOC/EOS Visit to assess treatment compliance.

Patients will be required to return the bottle containing 3 remaining doses of study treatment to the study site at the TOC/EOS Visit on Study Day 5. The number of remaining doses returned to the study site will be recorded on the patient's eCRF.

10.5 Study Treatment Accountability

Records shall be maintained of the delivery of study treatments to the study centers, the inventory at the study centers, distribution to and use of study drug by each patient and the return to the Sponsor, as well as the destruction of any study drug.

These records shall include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study drug and to the study patients.

The Investigator shall be responsible for ensuring that the records adequately document that the patients were provided the doses specified in the protocol and that all study drug received from the Sponsor is reconciled.

10.6 Concomitant Therapy

Concomitant medication will be allowed, with the exception of the prohibited medications noted below, or unless deemed otherwise by the Principal Investigator/Sub-Investigator.

The following concomitant medications are prohibited from the signing of informed consent until the TOC/EOS Visit on Study Day 5:

- any drug such as aspirin or ibuprofen (Advil) which can cause GI bleeding
- any medication considered "traditional" by the Investigator and that has an influence of GI function
- antimicrobial agents with an expected activity against enteric bacterial pathogens (e.g., trimethoprim/sulfamethoxazole, quinolones, azithromycin)
- oral antibiotic medications
- antimuscarinic drugs (e.g., Tolterodine, Solifenacin, Darifenacin, Trospium chloride), Oxybutynin. A complete list of commonly used medications with antimuscarinic effects is provided in Appendix II.

- drugs effecting GI motility such as antimotility agents, adsorbent agents, prokinetic agents and other stimulants of GI contractility, laxatives and cathartics, antacids, or anti-diarrheal agents
- analgesic drugs (opioids or non-steroidal anti-inflammatory drugs) NOTE: Use of paracetamol is allowed for a maximum of 2 consecutive days
- fiber products
- probiotics
- herbal products/dietary supplements with effect on the GI system (i.e., Rue [rude], wormwood, estafiate, Espazote de zorrillo, chamomile [manzanilla]).

The administration of any concomitant medication or herbal/dietary supplements during the study (from signing of informed consent until the TOC/EOS Visit) will be recorded by patients on the Supplemental Form provided at the Screening/Randomization Visit. The start and stop date should be recorded along with the reason for the medication use.

10.7 Complaints Connected to Study Drugs

10.7.1 Definitions

Quality complaints are complaints connected to the investigation's medicinal product (test product, reference product or placebo) and include:

- technical complaints are complaints connected to the quality of the products and include the following cases:
  - any fault of quality and/or effectiveness, e.g., change of visual appearance, change of amount, damaged tablets, presence of foreign matter
  - any fault of the labeling, e.g., missing or illegible label
  - any falsification of the medicinal product, e.g., suspected product mix-up, tampering or counterfeiting.
- transport complaints are complaints connected to the transport of the product, such as damaged transport carton, damaged packaging upon receipt of the shipment, missing drugs from the shipment package, unsuitable transport conditions.

10.7.2 Process

In case any of the above quality complaints are detected or received the completed Quality Complaint Report form must be sent to the Sponsor (study manager) within 24 hours. In parallel the local monitor or Clinical Research Associate of the respective study must be informed about the complaint. If possible, a photo of the affected material should be attached to the report. Affected material should be retained and stored according to the storage conditions label and/or returned to Sponsor if requested by the Sponsor.

11 ASSESSMENT OF EFFICACY

11.1 Efficacy Endpoints

11.1.1 Primary efficacy endpoint

The primary endpoint is clinical cure at the TOC/EOS Visit (Study Day 5 ± 1 day). Clinical cure is defined as either:

- no stools or only formed stools within a 48 hour period and no fever, with or without other enteric symptoms, OR
- no watery stools or no more than two soft stools passed within a 24 hour period with no fever and no other enteric symptoms except for mild excess gas/flatulence.

11.1.2 Secondary efficacy endpoints

- TLUS defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed
- proportion of patients with clinical failure defined as failure to achieve formed stool within ≤ 3 days (72 hours) of the start of treatment with the study drug or clinical deterioration or worsening of symptoms by Study Day 5 (± 1 day)
- proportion of patients with improvement of diarrheal syndrome, defined as reduction of ≥ 50% in the number of unformed stools (soft or watery) passed during the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug, compared to the number of unformed stools passed during the 24 hours immediately preceding first dose of study drug
- the number of unformed stools (soft or watery) passed during the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug
- the presence or absence and severity of signs and symptoms of enteric infection (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus) – the proportion of patients with signs and symptoms of enteric infection during the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug
- microbiological cure defined as a post-treatment culture that was negative for the pre-treatment etiologic pathogen.

11.2 Efficacy Assessments

11.2.1 Symptoms

Symptoms of TD to be noted include the presence or absence and severity of enteric symptoms (abdominal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus).

Patients will record the presence or absence and severity of any of these symptoms in the Patient Diary once daily, from the time of the Screening Visit until the TOC/EOS Visit on Study Day 5 (± 1 day).

11.2.2 Stool Frequency and Form

Patients will record in the Patient Diary the date, time and form of all stools passed, from the time of the first drug administration until the end of the study on Study Day 5 (± 1 day). Patients will receive detailed instructions, with diagrams, on how to rate the stool form.

Stools will be recorded as follows:

- formed (retains shape)
- soft (assumes shape of container)
- watery (can be poured).

Both soft and watery stools are to be considered unformed.

11.2.3 Microbiology

Stool specimens for quantification and identification of enteric pathogens will be taken on Study Day 0 as soon as possible after inclusion, prior to randomization and PRIOR to the first administration of study drug, and again on Study Day 5 (± 1 day).

Stool samples will be assessed in a central laboratory in order to determine the microbiological status of this acute diarrhea episode. Details on sample handling, collection, storage and shipping are provided in the laboratory manual.

Stools will be analyzed for the following:

- fecal leukocyte
- ETEC
- EAEC
- *Shigella* spp
- *Salmonella* spp
- *Campylobacter jejuni*
- *Plesiomonas* spp
- *Aeromonas* spp
- Rotavirus
- *Giardia lamblia*
- *Entamoeba histolytica*
- *Cryptosporidium* spp.

12 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in Section 9.1.2; the assessments are detailed in Sections 12.1 through 12.4.

Safety endpoints include incidence of reported AEs (Section 12.1), changes in vital signs (Section 12.3), and changes in clinical laboratory parameters (Section 12.4).

12.1 Adverse Events

12.1.1 Definitions

An adverse event/experience (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A **serious adverse event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing inpatient hospitalization
- is medically significant: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject (patient) or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious.

For further details, please refer to the **Quick Reference Guide for completing the Serious Adverse Event Form.**

An AE is defined as an **adverse drug reaction (ADR)** if the following applies:

- A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.
- ADRs may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include overdose, misuse, abuse and medication errors.
- Adverse events with a suspected relationship to non-investigational medicinal product or other concomitant medication (for both Sandoz and non-Sandoz products), even if non-serious, need to be reported by the Investigator to the respective Local Qualified Person for Pharmacovigilance (LPPV; Table 12-1).

12.1.2 Intensity of Adverse Events

In the course of the study, the Investigator will determine whether any AEs have occurred and will grade their intensity as follows:

- Mild: awareness of symptoms but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity
- Severe: incapacitating with inability to work or carry out usual activity.

12.1.3 Relationship to the Investigational Product

Assessment of AEs will be made by the Investigator after having evaluated all accessible data and, if necessary, re-evaluation of the case as new information becomes available. Investigational product includes the test product under evaluation and the reference product or placebo that is given during any phase of the study.

The Investigator will make a judgment considering whether or not, in his/her opinion, the AE was related to the drug according to the following classification:

Suspected:	The temporal relationship of the clinical event to study treatment administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
Not suspected:	The temporal relationship of the clinical event to study treatment administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Causality assessments are critical and must be provided for each unique event reported and for each study treatment or concomitant medication, if applicable. Missing causality assessments will be handled by the Sponsor as “suspected” to study treatment.

12.1.4 Adverse Events Documentation

Any AE (non-serious and serious) occurring after the patient has provided study-specific informed consent until the last study visit of the patient has to be recorded on the AE pages of the eCRF. The following information is to be recorded:

- verbatim/AE description
- time and date for AE start and stop
- maximum intensity
- seriousness
- causality rating
- action taken to treat AE
- action taken with study drug

- whether or not the AE caused the patient to discontinue
- outcome.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test or other assessments. All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug therapy given, patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be documented in the eCRF. In addition, the action taken with the study drug should be documented and be assigned to one of the following categories: not changed, withdrawn, reduced, increased, interrupted, unknown and not applicable. Concomitant medication, other treatments or changes in the administration of the study drug should be defined and be also documented.

Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after enrolment. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent. The outcome should be documented and be assigned to one of the following categories: not recovered/unchanged, condition deteriorating, recovered/resolved, improving/recovering, recovered/resolved with sequelae, fatal or unknown. The assessment of an AE should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship with the investigational product, the interventions required to treat it, and the outcome.

<u>AE/SAE between informed consent and first dosing</u>
Any AE/SAE occurring between study-specific informed consent and first dosing will be documented as *screening event* with a study drug causality assessment "*IMP not yet administered*".

<u>AE/SAE after first dosing</u>
All AEs/SAEs which occurred during the study are followed-up at the latest until the last visit of the patient. Then the last outcome assessment will be performed and documented in the eCRF.

For any ongoing AEs/SAEs at the time of last visit, the Investigator is obliged to follow-up with patient for safety reasons. All AEs ongoing at the time of the last patient visit should be followed up for 30 days after the last administration of study drug, with the exception of any ongoing study drug-related AEs, which should be followed until resolution, unless in the Investigator's opinion, the AE is unlikely to resolve due to the patient's underlying disease. The follow-up information (including the attempt to follow-up) is documented in source data (i.e., patient files). See also Section 12.1.5 for SAE follow-up reporting.

SAE after first dosing
If the outcome of a SAE is not resolved during the last visit of the patient, it is followed up by Sandoz on an individual basis until its resolution or until it is judged to be permanent.

AE at the final examination
Clinically relevant abnormal laboratory values detected at the final examination are to be documented as AEs, even when they cannot be attributed to treatment A or B, etc.

12.1.5 Serious Adverse Event (SAE) Reporting

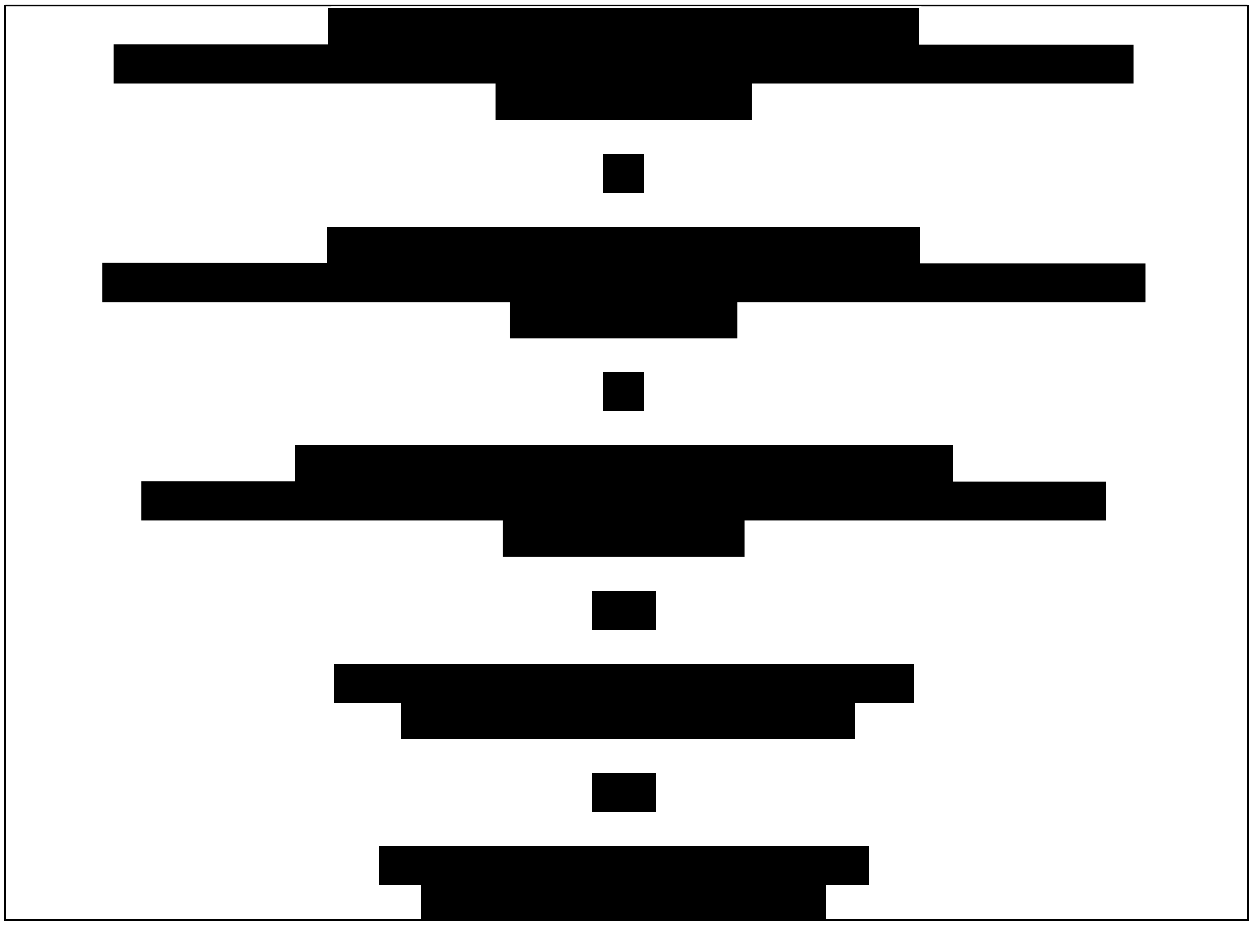
It is vitally important that the Investigator immediately reports any AE which by the definitions given above would be considered serious, even if the Investigator does not consider the AE to be drug-related.

All SAEs must be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. The Investigator is responsible for informing the EC of the SAE as per local requirements.

For reporting of a SAE, the Investigator should use the "Serious Adverse Event Report Form" (Novartis form). During the study the original of the SAE Report Form and all related correspondence (e.g. email print-out, fax confirmation sheet) must be kept with the eCRF at the study site.

Any SAE has to be **reported by the Investigator immediately** within 24 hours of learning of its occurrence, in the form of an initial report via fax or email to the LPPV, Sandoz and in copy to the responsible Study Manager (Sponsor) and the [redacted] maintaining a delivery notification for either system, as noted in Table 12-1.

Table 12-1 Serious Adverse Event Reporting Contacts



LPPV=Local Qualified Person for Pharmacovigilance

The responsible contact persons for questions are provided in Table 12-2.

Table 12-2 Contacts for General Safety Questions

Sponsor	

As soon as new information about the SAE becomes known, the Investigator has to forward it within 24 hours to the LPPV and in copy to the Study Manager (Sponsor), using a new SAE Report Form stating that this is a follow-up to the previously reported SAE. The follow-up information should describe whether the event has resolved or continues, if a diagnosis is available, if and how it was treated, and whether the patient continued or withdrew from study participation. Also queries on SAE reports should be answered by the Investigator

within 24 hours. For more detailed information refer to the "Quick Reference Guide for Completing the SAE Form" and the Manual for Completing the Novartis SAE Form for Clinical Trials" (Novartis documents).

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs.

A SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Any **SAE experienced after the final visit** of the patient should be reported to the LPPV and in copy to the responsible Study Manager (Sponsor), only if the Investigator suspects a causal relationship to the investigational product.

The unblinding of single cases by the Investigator in the course of the clinical trial should only be performed if relevant for the subsequent treatment of the patient in emergency situations (see also Section 10.3 on unblinding).

Investigator Notification and 6-Monthly Line Listings

If a SAE is not previously documented in the Reference Safety Information (Investigator's Brochure) and is thought to be related to the study drug, Sandoz may urgently require further information from the Investigator for Health Authority reporting. Sandoz may need to issue an Investigator Notification and, if applicable, 6 monthly line listings to inform all Investigators involved in any study with the same drug that this SAE has been reported. Sandoz will notify all reportable cases within the requested timelines to national authorities in order to fulfil the Sponsor´s reporting obligation.

The announcement of Investigator Notifications and 6-monthly line listings, if applicable, to local ECs is the responsibility of the Investigator as stipulated in the study contract. The announcement of Investigator Notifications and 6-monthly line listings to national EC is the responsibility of the Clinical Research Organization (CRO), if applicable.

Investigator Training

By his/her signature of the study protocol, the Investigator certifies that he/she has been trained in the Sandoz SAE/AE and pregnancy reporting obligations by the CRO as defined in the study protocol.

12.1.6 Pregnancies/Breastfeeding Cases

In general, all cases of drug exposure during pregnancy or drug use during lactation in patients exposed to Sandoz products, regardless of seriousness criteria or outcome, must be reported. Therefore, pregnancy cases of female patients or breastfeeding cases, which emerge during a clinical study between first dosing and the final visit, have to be reported by the Investigator to the Sponsor.

If a pregnancy of the female partners of male patients becomes known to the Investigator, which is likely to have started during study participation of the male patient (paternal exposure), this pregnancy will also need to be reported.

To ensure patient safety, each pregnancy or breastfeeding case in a patient participating in the study must be reported by the Investigator immediately within 24 hours of learning of its occurrence to the LPPV, Sandoz and in copy to the Study Manager (Sponsor), as described in Section12.1.5. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy or breastfeeding case should be recorded on a "Clinical Trial Pregnancy Form" (Novartis form) Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational product of any pregnancy outcome. For more detailed information refer to the "Clinical Trial Pregnancy Quick Reference Guide" (Novartis document).

Any SAE experienced during pregnancy must be reported on the SAE Report Form and reported as described in Section 12.1.5.

12.1.7 Quality Complaints or Special Case Scenarios

In case of quality complaints (technical or transport complaints), the Investigator within 24 hours of learning of its occurrence informs the Sponsor as described in Section 10.7. Any AE associated with a quality complaint needs to be documented and reported in addition by the Investigator as described in Sections 12.1.4 and 12.1.5.

Special case scenarios are always treated like AE cases, even if no other AEs have been reported. Special case scenarios can be assessed as serious or non-serious cases.

Some special case scenarios have to be reported within 24 hours from the Investigator to the LPPV, even if assessed as non-serious:

- pregnancy/breastfeeding (Section 12.1.6)
- withdrawal syndrome/reaction
- drug dependency, misuse, abuse or addiction (always serious)
- suspected transmission of infectious agents (always serious)
- use of a falsified product/counterfeit
- death (including without other event, always serious).

In cases where the Investigator suspects one of the following events (special case scenarios), the Sponsor has to be contacted likewise (within 24 hours for serious cases):

- medication error (including maladministration, accidental exposures and dispensing errors)
- occupational exposure
- pediatric or elderly exposure
- overdose (including suicide attempts; suicide attempt is always serious)
- lack of efficacy or vaccine failure (vaccine failure is always serious)
- drug/drug interactions
- disease progression or aggravation

- off-label use
- treatment non-compliance
- environmental issues (i.e. reported effects of pharmaceuticals on the environment, e.g. water contamination by pharmaceuticals).

12.1.8 Reconciliation

Reconciliation between the safety database of the Sponsor and the clinical database at the CRO will be done periodically as described in a reconciliation plan by comparing line listings from the safety database with the data in the clinical database.

The data management will review the eCRFs/clinical database for potentially unreported SAEs or other individual safety cases. For any Individual Safety Case Report, the following parameters need to match exactly between the clinical and the safety database: trial number, site number, patient number, randomization number (if applicable), investigational drug, seriousness, date of death (if applicable) and Investigator causality. All other parameters only need to be plausibly and medically consistent. For any SAE assessed as suspected, a more detailed reconciliation should be conducted, including treatment dates and medical history.

12.1.9 Abnormal Laboratory Values/Vital Signs

Laboratory/vital signs abnormalities should be reported as AEs if any one of the following criteria is met:

- any criterion for an SAE is fulfilled
- the laboratory/vital signs abnormality causes the patient to discontinue from the study treatment.
- the laboratory/vital signs abnormality causes the patient to interrupt the study treatment
- the laboratory/vital signs abnormality causes the patient to modify the dose of study treatment
- the Investigator believes that the abnormality should be reported as an AE
- if an abnormal laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom should be reported as an AE and the associated laboratory result or vital sign should be considered additional information that must be collected on the relevant eCRF.

12.2 Physical Examination

A full physical examination, including calculation of BMI, will be carried out at Study Day 1 and on Study Day 5 (± 1 day) at the TOC/EOS Visit. This examination will include assessment of the cardiovascular, GI and respiratory systems.

12.3 Vital Signs

Vital signs (respiratory rate, heart rate, blood pressure, and body temperature) will be assessed at the visits on Study Day 0 and Study Day 5 (± 1 day) according to the investigational sites standard of practice. Assessments will be carried out on patients in the

sitting position after the patient has rested for 5 minutes. The date and time of the assessment will be recorded.

12.4 Laboratory Assessments

Urine pregnancy tests will be done on all females of child bearing potential (not post-menopausal or not surgically sterile) prior to randomization at Study Day 1 and again on Study Day 5 (± 1 day). Urine pregnancy tests will be done locally.

Microbiological assessments of stool samples are detailed in Section 11.2.3.

All hematology, blood chemistry and urine samples will be analyzed at the central laboratory; details for handling, storage and shipping will be provided in the laboratory manual. Blood and urine samples will be collected for the following analyses:

- Hematology
  - hemoglobin
  - hematocrit
  - red blood cell count
  - platelet count
  - white blood cell count with differential
- Serum Chemistry
  - glucose
  - calcium
  - sodium
  - chloride
  - albumin
  - protein
  - bilirubin
  - blood urea nitrogen
  - lactate dehydrogenase
  - aspartate aminotransferase
  - alanine aminotransferase
  - potassium
  - alkaline phosphatase
  - uric acid
  - creatinine
  - creatine kinase
- Urinalysis
  - bilirubin
  - blood
  - glucose
  - pH
  - ketones

- leukocytes
- nitrites
- protein
- specific gravity
- urobilinogen

13 STATISTICAL EVALUATION

13.1 Sample Size and Power

According to the FDA Draft Guidance on rifaximin[11] sample sizes should be chosen such that the power is sufficient to establish therapeutic equivalence between generic and RLD rifaximin (Xifaxan) and sufficient to show that both are active compared to placebo (study sensitivity). Therapeutic equivalence is to be shown for the PP population whereas study sensitivity is to be shown for the modified Intent-to-Treat (mITT) population (Section 13.2.2).

A sample size of 135 in the generic rifaximin and 135 in the Xifaxan treatment groups achieve approximately [redacted] power to detect therapeutic equivalence when the margin of equivalence, given in terms of the difference, extends from -0.20 to 0.20. The calculations assume that:

- two one-sided Z tests (pooled) at the 0.05 significance level are used (corresponding to a 90% CI for the difference of success proportions);
- [redacted]
- [redacted]

Concerning the assessment of study sensitivity, a sample size of 170 in the rifaximin group, 170 in the Xifaxan group and 85 in the placebo group achieve approximately [redacted] power to detect a difference between the group proportions of [redacted], assuming that:

- [redacted]
- two-sided Z tests (pooled) at the 0.05 level will be used.

Patients will be randomized 2:2:1 to rifaximin (n=180), Xifaxan (n=180), and placebo (n=90). A total of 450 patients will be enrolled. As it can be anticipated that no more than 5% of patients will be excluded from the mITT population and no more than 20% of patients will be excluded from the PP population[12] this sample size will have sufficient power to show therapeutic equivalence and study sensitivity.

13.2 Statistical Methods

A detailed description of all statistical analyses to be performed for this study will be given in a statistical analysis plan (SAP). Any deviations from the analysis detailed in the protocol will be described in the SAP.

No interim analysis is planned.

Any deviations from the original SAP will be described and justified in the final CSR, as appropriate.

13.2.1 General Analysis and Coding

The statistical analysis will be performed using the software package SAS version 9.3 or higher (SAS Institute Inc., Cary, NC 27513, USA). All individual data as well as results of statistical analyses, whether explicitly discussed in the previous sections or not, will be presented in individual patient data listings and statistical summary tables.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Categorical data will be described using count and frequency. Shift tables will be provided, where appropriate. Confidence intervals will be two-sided 95% CIs if not otherwise specified.

All analyses and summary tables will be displayed by treatment group. Data to be used for comparability between treatment groups will be specified in the SAP.

The following international dictionaries (in latest available version) will be used for medical coding:

- Diagnoses: Medical Dictionary for Regulatory Activities (MedDRA)
- Medications: World Health Organization (WHO) Drug Dictionary including Anatomical Therapeutic Chemical (ATC) classification
- AEs: MedDRA

13.2.2 Analysis Populations

The following analysis populations will be defined for the statistical analyses:

- The Safety population will include all randomized patients who received at least 1 dose of the study product.
- The mITT population will include all randomized patients who met all inclusion/exclusion criteria, received at least 1 dose of the study drug and recorded the number of formed and unformed bowel movements during Study Day 1.
- The PP population will include all randomized patients from the mITT population who do not have a major protocol deviation that would affect treatment evaluation. Patients who discontinue the study due to lack of treatment effect after completing 3 days of treatment or whose condition worsens and who require alternate or supplemental therapy for the treatment of TD should be included in the PP population (see Section 13.2.5 for the handling of missing values).

Major protocol deviations include but are not limited to:

- lack of compliance defined as having administered <75% or >125% of the scheduled doses for the specified duration of the study
- completion of the TOC/EOS Visit outside the specified visit window (Study Day 5 ±1 day) (if patient did not discontinue the study due to lack of treatment effect or worsening of the underlying condition requiring alternate or supplemental therapy).

Further major protocol deviations will be defined in the SAP.

The PP population will be the primary population for establishing equivalence of rifaximin and Xifaxan regarding the primary efficacy endpoint (clinical cure). The mITT population will be the primary population for evaluation of the study sensitivity comparing the proportions of clinical cure between rifaximin and placebo and Xifaxan and placebo.

13.2.3 Primary Endpoint Analysis

The primary endpoint is clinical cure at the TOC/EOS Visit (Study Day 5 ± 1 day). Clinical cure is defined as either:

- No stools or only formed stools within a 48 hour period and no fever, with or without other enteric symptoms, OR
- No watery stools or no more than two soft stools passed within a 24 hour period with no fever and no other enteric symptoms except for mild excess gas/flatulence.

Patients will assess stool consistency and document it in the patient's diary; stools will be classified, as formed (retains shape), soft (assumes the shape of container), or watery (can be poured). When using this classification, both soft and watery stools are unformed and abnormal.

Therapeutic equivalence will be concluded if the 90% CI of the difference of the success proportions between rifaximin and Xifaxan is completely contained within the interval [-0.20; 0.20]. This approach can be alternatively formulated as a statistical test problem where the compound hypothesis to be tested is:

$$H_0: p_G - p_R < -0.20 \; or \; p_G - p_R > 0.20$$

against the alternative

$$H_1: -0.20 \leq p_G - p_R \leq 0.20$$

Here p_G denotes the probability of clinical cure at the TOC/EOS Visit for rifaximin and p_R denotes the respective probability for Xifaxan.

Two one-sided Z tests at the 0.05 significance level will be used for the above test problem. The PP population will be the primary analysis set for the assessment of therapeutic equivalence.

Study sensitivity will be evaluated by comparing the success proportions between rifaximin and placebo and Xifaxan and placebo. Two two-sided Z tests with pooled variance will be used. The significance level of each of these tests will be set to 0.05. The mITT population will be the primary analysis set for assessing study sensitivity.

The primary endpoint will also be analyzed by subgroups according to the pathogen status at baseline:

- inflammatory/invasive pathogens (i.e. *Campylobacter jejuni*, *Shigella* species, and *Salmonella* species)
- diarrheagenic *E Coli* group without evidence of inflammatory/invasive pathogens
- Other pathogens without evidence of inflammatory/invasive pathogens.

All p-values resulting from these subgroup analyses will be interpreted in the exploratory sense.

13.2.4 Secondary Endpoint Analysis

The analysis of all secondary endpoints will be performed in the mITT and PP populations.

13.2.4.1 Time to Last Unformed Stool

TLUS is defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed.

TLUS will be calculated for each patient in the following manner:

Step 1: Identify when the patient achieves clinical cure (definition see Section 13.2.3).

Step 2: Moving backwards from this time, identify the time of the last unformed stool.

Step 3: The TLUS equals the time from the first dose of study drug to the time of the last unformed stool identified in Step 2.

Patients who met the criteria for clinical cure (Section 13.2.3) immediately after the start of study drug and prior to passing any unformed stools will be defined as having a TLUS of 0 hours. Patients for whom TLUS cannot be calculated because they terminated early due to clinical failure (Section 13.2.4.2) will have censored TLUS of 120 hours. Patients who terminate early due to reasons other than clinical failure (AE, patient request, intercurrent illness) or because they completed the study without achieving clinical cure will have censored TLUS at the time of the last available information on unformed stools.

Rifaximin will be compared to Xifaxan, and the rifaximin groups to placebo using a Cox proportional hazards model with treatment group and center as independent variables. A treatment by center term will also be included to assess potential treatment by center interactions. Centers with 5 or fewer patients per treatment arm will be pooled with geographically related centers to form analysis centers.

13.2.4.2 Clinical Failure

Clinical failure is defined as failure to achieve formed stool within ≤ 3 days (72 hours) of the start of treatment with the study drug or clinical deterioration or worsening of symptoms by Study Day 5 (± 1 day, TOC/EOS Visit). The proportion of patients with clinical failure will be compared between the three treatment groups with two-sided Z tests. The significance level of these tests will be set to 0.05.

13.2.4.3 Diarrheal Syndrome

Improvement of diarrheal syndrome is defined as reduction of ≥ 50% in the number of unformed stools (soft or watery) passed during a 24-hour post-enrolment interval (the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug) compared to number of unformed stools passed during the 24 hours immediately preceding the first dose of study drug. The proportion of patients with

improvement of diarrheal syndrome will be compared between the three treatment groups with two-sided Z tests. The significance level of these tests will be set to 0.05.

13.2.4.4 Unformed Stools

The number of unformed stools (soft or watery) passed during the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug will be compared between the three groups using repeated measures Poisson regression with treatment, time, and interaction as fixed effects, and with the baseline number of unformed stools as a covariate In the event that the data are overdispersed, a negative binomial model will be used.

13.2.4.5 Signs and Symptoms of Enteric Infection

The proportion of patients with the presence or absence and severity of signs and symptoms of enteric infection (abnormal pain/cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, tenesmus) during the intervals 0-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, and 96-120 hours after the first dose of study drug will be compared between the three treatment groups with two-sided Z tests. The significance level of these tests will be set to 0.05.

13.2.4.6 Microbiological Cure

Microbiological cure is defined as a post-treatment culture that is negative for the pre-treatment etiologic pathogen. For those patients with a positive pre-treatment culture the proportion of patients with microbiological cure will be compared between the three treatment groups with two-sided Z tests. The significance level of these tests will be set to 0.05. This test will be considered as supportive of the similarity of populations in each arm of the study and not considered as evidence of equivalence.

13.2.5 Handling Missing Data

Patients who are discontinued early from the study due to lack of treatment effect after completing 3 days of treatment should be included in the PP population using the last observation carried forward (LOCF). Patients whose condition worsens and who require alternate or supplemental therapy for the treatment of TD should be discontinued, included in the PP population analysis using LOCF, and provided with effective treatment. Patients discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF.

13.2.6 Patient Disposition

The primary reason for withdrawal will be summarized by treatment group in the safety population.

13.2.7 Safety Analyses

The safety evaluations will include analyses of AEs, vital signs, safety laboratory measurements, and physical examinations. The analysis of safety will be based on the safety population.

13.2.7.1 Adverse Events

The incidence of treatment-emergent AEs will be summarized for each treatment group by MedDRA system organ class (SOC) and preferred term. An AE is defined as treatment-emergent if its onset date/time is on or after the date/time of the first intake of study mediation or if a pre-existing condition becomes worse after the date/time of first intake of study drug. An AE is defined as pre-treatment if its onset date/time is before the date/time of the first intake of study mediation. AEs will be summarized according to the following:

- An overview of the absolute and relative frequencies of patients with at least one AE will be given for the categories pre-treatment and treatment-emergent by seriousness, severity, and causality.
- Further tables will present the absolute and relative frequencies of patients with at least one treatment-emergent AE classified by SOC and preferred term and, in addition, by seriousness and causality.
- The absolute and relative frequencies of patients with at least one related treatment-emergent AE will be summarized by SOC and preferred term. An AE will be defined as related if its causality is either probable or possible.
- The absolute and relative frequencies of patients with at least one SAE will be summarized by SOC and preferred term.
- The absolute and relative frequencies of patients with at least one AE leading to discontinuation of study drug will be summarized by SOC and preferred term.
- Individual patient data listings will be provided for all deaths, patients with other SAEs, and discontinuation of study drug due to AEs.

Regarding the summaries by severity and causality the following rule will be applied: if a patient experiences more than one AE within the same SOC or with the same preferred term, the AE with the highest severity (closest relationship to study treatment) will be used for the analysis.

13.2.7.2 Vital Signs

Vital signs (body temperature, blood pressure, heart rate, respiratory rate) will be analyzed in the following way:

- Standard descriptive summary statistics will be calculated at each scheduled time point and the last individual time point.
- Further, standard descriptive summary statistics will be computed for the absolute change from baseline to each scheduled time point after baseline and the last individual time point.
- A patient data listing of all clinically significant abnormal vital signs will be provided.

13.2.7.3 Laboratory Parameters

Laboratory data will be subjected to both a quantitative analysis (descriptive summary statistics) and qualitative analysis where frequencies of normal, abnormal low, and abnormal high values will be computed.

The following analyses will be performed:

- Standard descriptive summary statistics will be calculated at each scheduled measuring time point and the last individual measuring time point.
- Standard descriptive summary statistics will be calculated for the absolute and relative change from baseline to each scheduled measuring time point after baseline and the last individual measuring time point.
- Shift tables displaying changes with respect to the normal range between baseline and each scheduled measuring time point after baseline and the last individual measuring time point will be provided.
- A listing of all patients with abnormal values at any time point will be given.

13.2.7.4 Physical Examinations

The results of physical examinations will be presented in individual patient listings.

14 DIRECT ACCESS TO SOURCE DATA/NOTES

Information on the eCRF should be verifiable to source documents. Other records that will be considered source documents include, but are not limited to, electronic Patient Diary, hospital records, clinic charts, radiographic data, laboratory reports and pathology reports. Copies of source documents that should be sent to the Sponsor or Sponsor's authorized representative, if requested, include operative summaries and discharge reports. Other source documents may include hospital discharge summaries, if available, or information in lieu of a discharge summary, such as discharge orders or progress notes; any relevant notes pertaining to AEs, additional surgical procedures, or deaths and autopsy reports.

The Investigator must maintain a copy of all data collected for each patient treated (including eCRF, eDiary and source data). In order to assure the accuracy of data collected in the eCRF, it is mandatory that the representatives of the Sponsor (or designee) as well as representatives of the regulatory authorities and the ECs have direct access to original source documents (e.g., patient records, patient charts, laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality and regulatory requirements.

The Investigator shall arrange the retention of the patient identification codes and Investigator's trial files for at least 15 years after the completion or discontinuation of the study. Patient files and other source data shall be retained in accordance with national legislation and in the accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator must retain essential documents as specified in Section 18.4. No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

The Sponsor reserves the right to terminate the study for refusal of the Investigator to supply source documentation of work performed in the study.

15 PATIENT CONFIDENTIALITY

Patient names shall not be revealed to the Sponsor or Sponsor's authorized representatives. Only the patient identifier and initials will be recorded in the eCRF, and if the patient's name appears on any other document, it must be redacted and replaced with the patient identifier before a copy of the document is supplied to the Sponsor or Sponsor's authorized representatives. In the event of accidental communication of such information, immediate steps to redact the information from all study files will be implemented, with appropriate documentation in the patient study file.

Study findings stored on a computer will be stored in accordance with local data protection laws.

By signing the ICF, patients give explicit permission for representatives of the Sponsor, regulatory authorities, and the EC to have direct access to their medical records to verify the information collected. Patients will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with laws and regulations.

All personnel involved in the study will observe and work within the confines of local data protection regulations.

16 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Conduct of the Study

[redacted] shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013) and all revisions thereof, and in accordance with FDA regulations (Code of Federal Regulations [CFR], Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate EC, except when necessary to eliminate immediate hazards to the patient. Any deviations may result in the patient having to be withdrawn from the study and render that patient non-evaluable.

16.2 Study Monitoring

The Investigator shall permit the Site Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall access medical records for the Monitor in order that entries in the eCRF may be verified. The Investigator, as part of his/her responsibilities, is expected to co-operate with [redacted] in ensuring that the study adheres to GCP requirements.

Monitors will perform 100% source data verification to confirm that the data recorded in the eCRF reported data are accurate, complete and verifiable from the medical/study records of each patient; the presence of appropriately signed and dated ICF; adherence to inclusion/exclusion criteria; and documentation of all SAEs.

The Investigator may not recruit patients into the study until such time that a visit, or with the agreement of the Sponsor, attendance at the Investigator meeting, has been made by a Sponsor/[redacted] monitor to conduct a detailed review of the protocol and eCRF.

17 ETHICS

17.1 Ethics Committee

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant EC. The EC shall be appropriately constituted and perform its functions in accordance with FDA ICH GCP and local requirements as applicable.

The EC shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures (e.g., advertisements), written information to be provided to the patients, Investigator's Brochure, available safety information, information about payment and compensation available to patients, the Investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the EC and Regulatory Authority (Competent Authority) as applicable.

17.2 Regulatory Authority

Beside other study relevant documents, the appropriate information about the active compound (e.g., Investigator’s Brochure); the protocol; name and site of the Investigators; and the vote of the ECs will be submitted to the relevant competent authorities before starting the study in compliance with the Declaration of Helsinki, the ICH-GCP guidelines and the national laws and regulations. In accordance with the national law all approvals needed for conduction of the trial in this country will be obtained. The trial can start after the approval is granted.

17.3 Written Informed Consent

The nature and purpose of the study shall be fully explained to each patient in a form understandable to them; the Investigator must confirm that the patient is able to understand the language of the ICF and Patient Information. The process of obtaining informed consent will be in compliance with relevant regulatory guidance, ICH requirements and local laws. The consent documents to be used for the study shall be reviewed and approved by the appropriate EC prior to use.

Signed and dated informed consent must be obtained from each patient prior to any study procedures being performed. The Investigator or Investigator’s designee will provide background information on the study, including the benefits and risks of both the investigative treatment, control treatment and the implications of possible enrolment to placebo; scope of the study; procedures to be done at each visit; and responsibility of the patient (e.g., completion of the Patient Diary). The Investigator or Investigator’s designee will also encourage the prospective patient to ask questions about the study and will provide the prospective patient with sufficient opportunity to consider whether or not to participate.

Original signed and dated ICFs must be filed in the patient records at the site. A copy of the signed and dated consent must also be provided to the patient or to his/her legal representative.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to all new patients and repeat the consent process with the amended ICF for any ongoing patients, if appropriate.

18 DATA HANDLING AND RECORD KEEPING

18.1 Case Report Forms/Source Data Handling

The Investigator shall be provided with standardized eCRFs and shall ensure that all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign each eCRF to verify the integrity of the data recorded.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. It is essential that all samples be analyzed at the central laboratory.

The Investigator must maintain source documents, such as laboratory reports, consultation reports, and complete medical history and physical examination reports (Section 14).

18.2 Patient Diaries

Patients will be provided with electronic Diaries, and instructed in how to use and complete the Diary entries at Visit 1 (Screening and Randomization). Investigators must ensure that the patient is able to understand the instructions, and be able to read the language of the Diary provided. Patients who are not able to understand the instructions, or complete the Diary entries, will not be enrolled into the study.

18.3 Investigator File

The Investigator/institution should maintain an Investigator Trial File specific for the study and clinical center. The Investigator/institution must maintain trial-related documents per ICH E6§8 and 21CRF 312.57, and must take measures to prevent accidental or premature destruction of these documents. Sites should archive Investigator Files at least for 15 years after study close-out at the site.

18.4 Retention of Essential Documents/Materials

18.4.1 Essential Documents

Essential documents should be retained for at least 15 years after the end of study. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Details and instructions for collection, handling, shipping and storage of retention samples (Section 18.4.2) will be provided in the laboratory manual.

18.4.2 Essential Materials

Retention samples of all study treatments will be stored in national depots, per 21 CFR 320.38, 320.63; 21 CFR 320.36; 21 CFR 58; Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”; and ICH E6, “Good Clinical Practice: Consolidated

Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP).

Retention samples will be randomly selected from the drug supplies received prior to dispensing to study centers.

Details and instructions for collection, handling, shipping and storage of retention samples will be provided in the laboratory manual. The samples will be stored until the Sponsor confirms storage is no longer required and regulatory requirements for storage times have been met. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used (21 CFR 320.38).

Retention samples will not be returned to the Sponsor at any time.

19 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate clinical study agreement.

The Sponsor will provide clinical trial liability insurance for study patients in all participating countries according to the local regulations.

20 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data.

When the study is complete the Sponsor shall arrange the analysis and tabulation of data. A CSR shall then be prepared, which may be used by the Sponsor for publication, presentation at scientific meetings or submission to regulatory authorities.

Individual Investigators and/or their associates subsequently may publish additional findings of the study. All publications (manuscripts, abstracts or other modes of presentation) shall be submitted at a time determined by the Sponsor and must be reviewed and approved in writing by the Sponsor, in advance of submission. Co-authorship with any Sponsor personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

21 REFERENCE LIST

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12. Taylor DN, Bourgeois AL, Ericsson CD, Steffen R, Jiang Z-D, Halpren J, Haake R, Dupont HL. A randomized, double-blind, multicenter study of rifaximin compared with placebo and with ciprofloxacin in the treatment of travelers' diarrhea. Am J Trop Med Hyg. 2006;74:1060–66.

22 APPENDICES

Appendix I Xifaxan Prescribing Information

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, for oral use
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
Irritable Bowel Syndrome with Diarrhea (1.3) 5/2015
Dosage and Administration
Irritable Bowel Syndrome with Diarrhea (2.3) 5/2015

INDICATIONS AND USAGE

XIFAXAN is a rifamycin antibacterial indicated for:

- Treatment of travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adult and pediatric patients 12 years of age and older (1.1)
- Reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults (1.2)
- Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults (1.3)

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, 5.1)

DOSAGE AND ADMINISTRATION

Condition	*Recommended Dosage Regimen*
TD (2.1)	One 200 mg tablet 3 times a day for 3 days
HE (2.2)	One 550 mg tablet 2 times a day
IBS-D (2.3)	One 550 mg tablet 3 times a day for 14 days. Patients who experience recurrence can be retreated up to two times with the same regimen.

- XIFAXAN can be taken with or without food. (2.4)

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)

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 to 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 Class C) hepatic impairment (5.4, 8.7)
- Concomitant P-glycoprotein inhibitor: Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor is needed (5.5, 7.2).

ADVERSE REACTIONS

Most common adverse reactions:

- TD (≥2%): Headache (6.1)
- HE (≥10%): Peripheral edema, nausea, dizziness, fatigue, and ascites (6.1)
- IBS-D (≥2%): ALT increased, nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-508-0024 and www.Salix.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 is indicated for the treatment of travelers' diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adults and pediatric patients 12 years of age and older.

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 [see Warnings and Precautions (5.1), Clinical Pharmacology (12.4), Clinical Studies (14.1)]*.

1.2 Hepatic Encephalopathy

XIFAXAN is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults.

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)]*.

1.3 Irritable Bowel Syndrome with Diarrhea

XIFAXAN is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

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.

2.2 Dosage for Hepatic Encephalopathy

The recommended dose of XIFAXAN is one 550 mg tablet taken orally two times a day.

2.3 Dosage for Irritable Bowel Syndrome with Diarrhea

The recommended dose of XIFAXAN is one 550 mg tablet taken orally three times a day for 14 days. Patients who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen.

2.4 Administration

XIFAXAN can be taken 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

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 to 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 *[see Indications and Usage (1.1)]*.

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 Class C) Hepatic Impairment

There is increased systemic exposure 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 Class C) *[see Use in Specific Populations (8.7), Clinical Studies (14.2)]*.

5.5 Concomitant use with P-glycoprotein Inhibitors

Concomitant administration of drugs that are P-glycoprotein inhibitors with XIFAXAN can substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor such as cyclosporine is needed. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-glycoprotein inhibitors may further increase the systemic exposure to rifaximin *[see Drug Interactions (7.2), Pharmacokinetics (12.3)]*.

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 irritation.

The adverse reaction that occurred at a frequency ≥2% in XIFAXAN-treated patients (n=320) at a higher rate than placebo (n=228) the two placebo-controlled trials of TD was:

- headache (10% XIFAXAN, 9% placebo)

Hepatic Encephalopathy

The data described below reflect exposure to XIFAXAN 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 (range: 21 to 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. The most common adverse reactions that occurred at an incidence ≥5% and at a higher incidence in XIFAXAN-treated subjects than in the placebo group in the 6-month trial are provided in Table 1.

Table 1: Most Common Adverse Reactions[1] in HE Trial

	Number (%) of Patients	
MedDRA Preferred Term	**XIFAXAN Tablets 550 mg TWICE DAILY**	**Placebo n=159**

	n=140	
Peripheral edema	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%)
Anemia	11 (8%)	6 (4%)
Depression	10 (7%)	8 (5%)
Nasopharyngitis	10 (7%)	10 (6%)
Abdominal pain upper	9 (6%)	8 (5%)
Arthralgia	9 (6%)	4 (3%)
Dyspnea	9 (6%)	7 (4%)
Pyrexia	9 (6%)	5 (3%)
Rash	7 (5%)	6 (4%)

1. reported in ≥5% of Patients Receiving XIFAXAN and at a higher incidence than placebo

Irritable Bowel Syndrome with Diarrhea

The safety of XIFAXAN for the treatment of IBS-D was evaluated in 3 placebo-controlled studies in which 952 patients were randomized to XIFAXAN 550 mg three times a day for 14 days. Across the 3 studies, 96% of patients received at least 14 days of treatment with XIFAXAN. In Trials 1 and 2, 624 patients received only one 14-day treatment. Trial 3 evaluated the safety of XIFAXAN in 328 patients who received 1 open-label treatment and 2 double-blind repeat treatments of 14 days each over a period of up to 46 weeks. The combined population studied had a mean age of 47 (range: 18 to 88) years of whom approximately 11% of the patients were ≥65 years old, 72% were female, 88% were White, 9% were Black and 12% were Hispanic.

The adverse reaction that occurred at a frequency ≥2% in XIFAXAN-treated patients at a higher rate than placebo in Trials 1 and 2 for IBS-D was:

- nausea (3% XIFAXAN, 2% placebo)

The adverse reactions that occurred at a frequency ≥2% in XIFAXAN-treated patients (n=328) at a higher rate than placebo (n=308) in Trial 3 for IBS-D during the double-blind treatment phase were:

- ALT increased (XIFAXAN 2%, placebo 1%)
- nausea (XIFAXAN 2%, placebo 1%)

Less Common Adverse Reactions

The following adverse reactions, presented by body system, were reported in less than 2% of patients in clinical trials of TD and IBS-D and in less than 5% of patients in clinical trials of HE:

Hepatobiliary disorders: Clostridium colitis

Investigations: Increased blood creatine phosphokinase

Musculoskeletal and connective tissue disorders: myalgia

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

7.1 Effects of XIFAXAN on Other Drugs

Substrates of Cytochrome P450 enzymes

Rifaximin is not expected to inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 in clinical use based on *in vitro* studies *[see Clinical Pharmacology (12.3)]*.

An *in vitro* study has suggested that rifaximin induces CYP3A4 *[see Clinical Pharmacology (12.3)]*. However, in patients with normal liver function, XIFAXAN 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.

7.2 Effects of Other Drugs on XIFAXAN

In vitro studies suggested that rifaximin is a substrate of P-glycoprotein, OATP1A2, OATP1B1 and OATP1B3. Concomitant cyclosporine, an inhibitor of P-glycoprotein and OATPs significantly increased the systemic exposure to rifaximin.

Cyclosporine

Co-administration of cyclosporine, with XIFAXAN resulted in 83-fold and 124-fold increases in rifaximin mean C_{max} and AUC_{∞} in healthy subjects. The clinical significance of this increase in systemic exposure is unknown *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on XIFAXAN use in pregnant women to inform any drug associated risks. Teratogenic effects were observed in animal reproduction studies following administration of rifaximin to pregnant rats and rabbits during organogenesis at doses approximately 0.9 to 5 times and 0.7 to 33 times, respectively of the recommended human doses of 600 mg to 1650 mg per day. In rabbits, ocular, oral and maxillofacial, cardiac, and lumbar spine malformations were observed. Ocular malformations were observed in both rats and rabbits at doses that caused reduced maternal body weight gain *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and

miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

Rifaximin was teratogenic in rats at doses of 150 to 300 mg/kg (approximately 2.5 to 5 times the recommended dose for TD [600 mg per day], and approximately 1.3 to 2.6 times the recommended dose for HE [1100 mg per day], and approximately 0.9 to 1.8 times the recommended dose for IBS-D [1650 mg per day] adjusted for body surface area). Rifaximin was teratogenic in rabbits at doses of 62.5 to 1000 mg/kg (approximately 2 to 33 times the recommended dose for TD [600 mg per day], and approximately 1.1 to 18 times the recommended dose for HE [1100 mg per day], and approximately 0.7 to 12 times the recommended dose for IBS-D [1650 mg per day] adjusted for body surface area). These effects include cleft palate, agnathia, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae.

A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses of rifaximin up to 300 mg/kg per day (approximately 5 times the recommended dose for TD [600 mg per day], and approximately 2.6 times the recommended dose for HE [1100 mg per day], and approximately 1.8 times the recommended dose for IBS-D [1650 mg per day] adjusted for body surface area).

8.2 Lactation

Risk Summary

There is no information regarding the presence of rifaximin in human milk, the effects of rifaximin on the breastfed infant, or the effects of rifaximin on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for XIFAXAN and any potential adverse effects on the breastfed infant from XIFAXAN or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of XIFAXAN has not been established in pediatric patients less than 12 years of age with TD or in patients less than 18 years of age for HE and IBS-D.

8.5 Geriatric Use

Of the total number of patients in the clinical study of XIFAXAN for HE, 19% of patients were 65 and over, while 2% were 75 and over. In the clinical studies of IBS-D, 11% of patients were 65 and over, while 2% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects for either indication. Clinical studies with XIFAXAN for TD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects. 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-, 14-, and 21-fold higher in those patients with mild (Child-

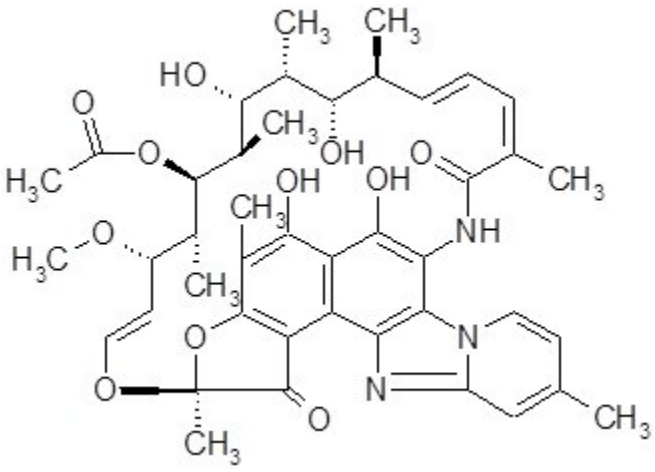
Pugh Class A), moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, respectively, compared to that in healthy volunteers. No dosage adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when XIFAXAN is administered to patients with severe hepatic impairment *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3), 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 (greater than 600 mg per day for TD, greater than 1100 mg per day for HE or greater than 1650 mg per day for IBS-D), 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 200 mg tablet contains colloidal silicon dioxide, disodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

Each 550 mg tablet contains colloidal silicon dioxide, glycerol palmitostearate, microcrystalline cellulose, polyethylene glycol/macrogol, polyvinyl alcohol, 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

In healthy subjects, the mean time to reach peak rifaximin plasma concentrations was about an hour and the mean C_{max} ranged 2.4 to 4 ng/mL after a single dose and multiple doses of XIFAXAN 550 mg.

Travelers' Diarrhea

Systemic absorption of XIFAXAN (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

Mean rifaximin exposure (AUC_τ) in patients with a history of HE was approximately 12-fold higher than that observed in healthy subjects. Among patients with a history of HE, 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 Warnings and Precautions (5.4) and Use in Specific Populations (8.7)]*.

Irritable Bowel Syndrome with Diarrhea

In patients with irritable bowel syndrome with diarrhea (IBS-D) treated with XIFAXAN 550 mg three times a day for 14 days, the median T_{max} was 1 hour and mean C_{max} and AUC were generally comparable with those in healthy subjects. After multiple doses, AUC_{tau} was 1.65-fold higher than that on Day 1 in IBS-D patients (Table 2).

Table 2. Mean (± SD) Pharmacokinetic Parameters of Rifaximin Following XIFAXAN 550 mg Three Times a Day in IBS-D Patients and Healthy Subjects

	Healthy Subjects		IBS-D Patients	
	Single-Dose (Day 1) n=12	**Multiple-Dose (Day 14) n=14**	**Single-Dose (Day 1) n=24**	**Multiple-Dose (Day 14) n=24**
C_{max} (ng/mL)	4.04 (1.51)	2.39 (1.28)	3.49 (1.36)	4.22 (2.66)
T_{max} (h)[1]	0.75 (0.5-2.1)	1.00 (0.5-2.0)	0.78 (0-2)	1.00 (0.5-2)
AUC_{tau} (ng•h/mL)	10.4 (3.47)	9.30 (2.7)	9.69 (4.16)	16.0 (9.59)
Half-life (h)	1.83 (1.38)	5.63 (5.27)	3.14 (1.71)	6.08 (1.68)

1. 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 but did not significantly affect C_{max}.

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 was administered.

Elimination

The mean half-life of rifaximin in healthy subjects at steady-state was 5.6 hours and was 6 hours in IBS-D patients.

Metabolism:

In an *in vitro* study rifaximin was metabolized mainly by CYP3A4. Rifaximin accounted for 18% of radioactivity in plasma suggesting that the absorbed rifaximin undergoes extensive metabolism.

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 mostly as the unchanged drug and 0.32% was recovered in urine mostly as metabolites with 0.03% as the unchanged drug.

Biliary excretion of rifaximin was suggested by a separate study in which rifaximin was detected in the bile after cholecystectomy in patients with intact gastrointestinal mucosa.

Specific Populations

Hepatic Impairment

The systemic exposure of rifaximin was markedly elevated in patients with hepatic impairment compared to healthy subjects.

The pharmacokinetics of rifaximin in patients with a history of HE was evaluated after administration of XIFAXAN 550 mg twice a day. The pharmacokinetic parameters were associated with a high variability and mean rifaximin exposure (AUC_τ) in patients with a history of HE was higher compared to those in healthy subjects. The mean AUC_τ in patients with hepatic impairment of Child-Pugh Class A, B, and C was 10-, 14-, and 21-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=15)	C (n=6)
AUC_{tau} (ng•h/mL)	12.3 ± 4.8	118 ± 67.8	169 ± 55.7	257 ± 100.2
C_{max} (ng/mL)	3.4 ± 1.6	19.5 ± 11.4	25.4 ± 11.9	39.7 ± 13.4
T_{max}[2] (h)	0.8 (0.5, 4.0)	1 (0.9, 10)	1 (1.0, 4.2)	1 (0, 2)

1. Cross-study comparison with pharmacokinetic parameters in healthy subjects
2. Median (range)

Renal Impairment

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

Drug Interaction Studies

Effect of other drugs on rifaximin

An *in vitro* study suggests that rifaximin is a substrate of CYP3A4.

In vitro rifaximin is a substrate of P-glycoprotein, OATP1A2, OATP1B1, and OATP1B3. Rifaximin is not a substrate of OATP2B1.

Cyclosporine

In vitro in the presence of P-glycoprotein inhibitor, verapamil, the efflux ratio of rifaximin was reduced greater than 50%. In a clinical drug interaction study, mean C_{max} for rifaximin was increased 83-fold, from 0.48 to 40.0 ng/mL; mean AUC_{∞} was increased 124-fold, from 2.54 to 314 ng●h/mL following co-administration of a single dose of XIFAXAN 550 mg with a single 600 mg dose of cyclosporine, an inhibitor of P-glycoprotein *[see Drug Interactions (7.2)]*.

Cyclosporine is also an inhibitor of OATP, breast cancer resistance protein (BCRP) and a weak inhibitor of CYP3A4. The relative contribution of inhibition of each transporter by cyclosporine to the increase in rifaximin exposure is unknown.

Effect of rifaximin on other drugs

In *in vitro* drug interaction studies the IC_{50} values for rifaximin was >50 micromolar (~60 mcg) for CYP isoforms 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, and 2E1. *In vitro* IC_{50} value of rifaximin for CYP3A4 was 25 micromolar. Based on *in vitro* studies, clinically significant drug interaction via inhibition of 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4 by rifaximin is not expected.

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

In *in vitro* studies, rifaximin at 3 micromolar inhibited the uptake of estradiol glucuronide via OATP1B1 by 64% and via OATP1B3 by 70% while the uptake of estrone sulfate via OATP1A2 was inhibited by 40%. The inhibitory potential of rifaximin on these transporters at the clinically relevant concentrations is unknown.

Midazolam

In an *in vitro* study, rifaximin was shown to induce CYP3A4 at the concentration of 0.2 micromolar. No significant induction of CYP3A4 enzyme using midazolam as a substrate was observed when rifaximin was administered three times a day for 7 days at 200 mg and 550 mg doses in two clinical drug interaction studies in healthy subjects.

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

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

Oral Contraceptives Containing Ethinyl Estradiol and Norgestimate

The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if XIFAXAN 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 XIFAXAN.

An open-label oral contraceptive study was conducted in 39 healthy female subjects to determine if XIFAXAN 550 mg orally administered three times a day for 7 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.025 mg of ethinyl estradiol (EE) and 0.25 mg norgestimate (NGM). Mean C_{max} of EE and NGM was lower by 25% and 13%, after the 7-day XIFAXAN regimen than when the oral contraceptive was given alone. The mean AUC values of NGM active metabolites were lower by 7% to approximately 11%, while AUC of EE was not altered in presence of rifaximin. The clinical relevance of the C_{max} and AUC reductions in the presence of rifaximin is not known.

12.4 Microbiology

Mechanism of Action

Rifaximin is a semi-synthetic derivative of rifampin and acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase blocking one of the steps in transcription. This results in inhibition of bacterial protein synthesis and consequently inhibits the growth of bacteria.

Drug Resistance and Cross-Resistance

Resistance to rifaximin is caused primarily by mutations in the *rpoB* gene. This changes the binding site on DNA dependent RNA polymerase and decreases rifaximin binding affinity, thereby reducing efficacy. Cross-resistance between rifaximin and other classes of antimicrobials has not been observed.

Antibacterial Activity

Rifaximin has been shown to be active against the following pathogens both *in vitro* and in clinical studies of infectious diarrhea as described in the *Indications and Usage (1.1)* section:

Escherichia coli (enterotoxigenic and enteroaggregative strains).

Susceptibility Tests

In vitro susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI).[1,2,3] 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 per day (doses equivalent to 2.4 to 4 times the recommended dose of 200 mg three times daily for TD, and equivalent to 1.3 to 2.2 times the recommended dose of 550 mg twice daily for HE, 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 per day (doses equivalent to 1.2 to 16 times the recommended daily dose for TD and equivalent to 0.7 to 9 times the recommended daily dose for HE, 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 per day for TD, and approximately 2.6 times the clinical dose of 1100 mg per day for HE, adjusted for body surface area).

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 4 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 4. Clinical Response in Study 1 (ITT population)

	XIFAXAN (n=125)	Placebo (n=129)	Estimate (97.5% CI)
Median TLUS (hours)	32.5	58.6	2[1] (1.26, 2.50)
Clinical cure, n (%)	99 (79)	78 (60)	19[2] (5.3, 32.1)

1. Hazard Ratio (p-value <0.001)
2. Difference in rates (p-value <0.01)

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

	XIFAXAN	Placebo
Overall	48/70 (69)	41/61 (67)
E. coli	38/53 (72)	40/54 (74)

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.

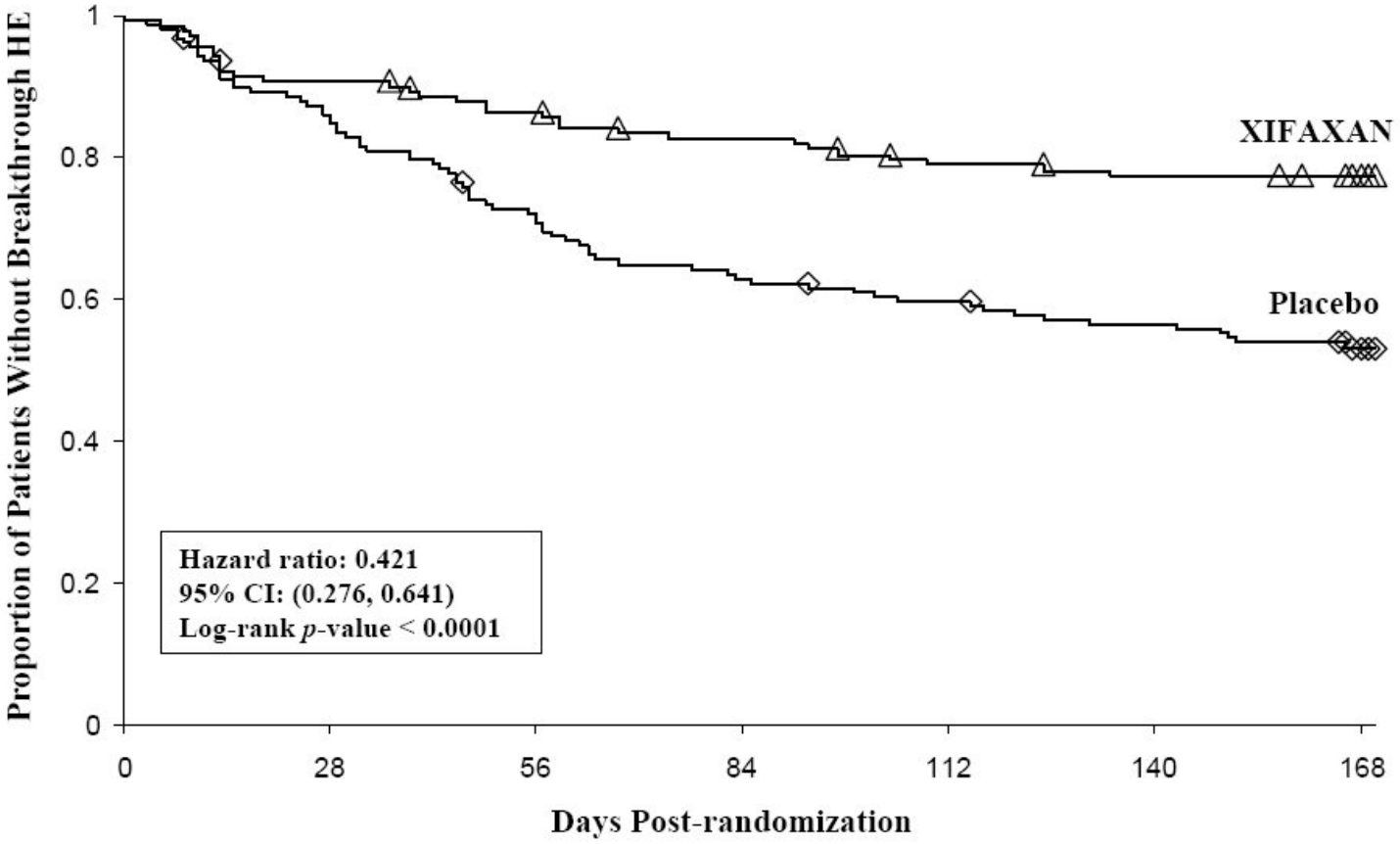


Figure 1 Kaplan-Meier Event-Free Curves1 in HE Study (Time to First Breakthrough-HE Episode up to 6 Months of Treatment, Day 170) (ITT Population)

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 Class 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.

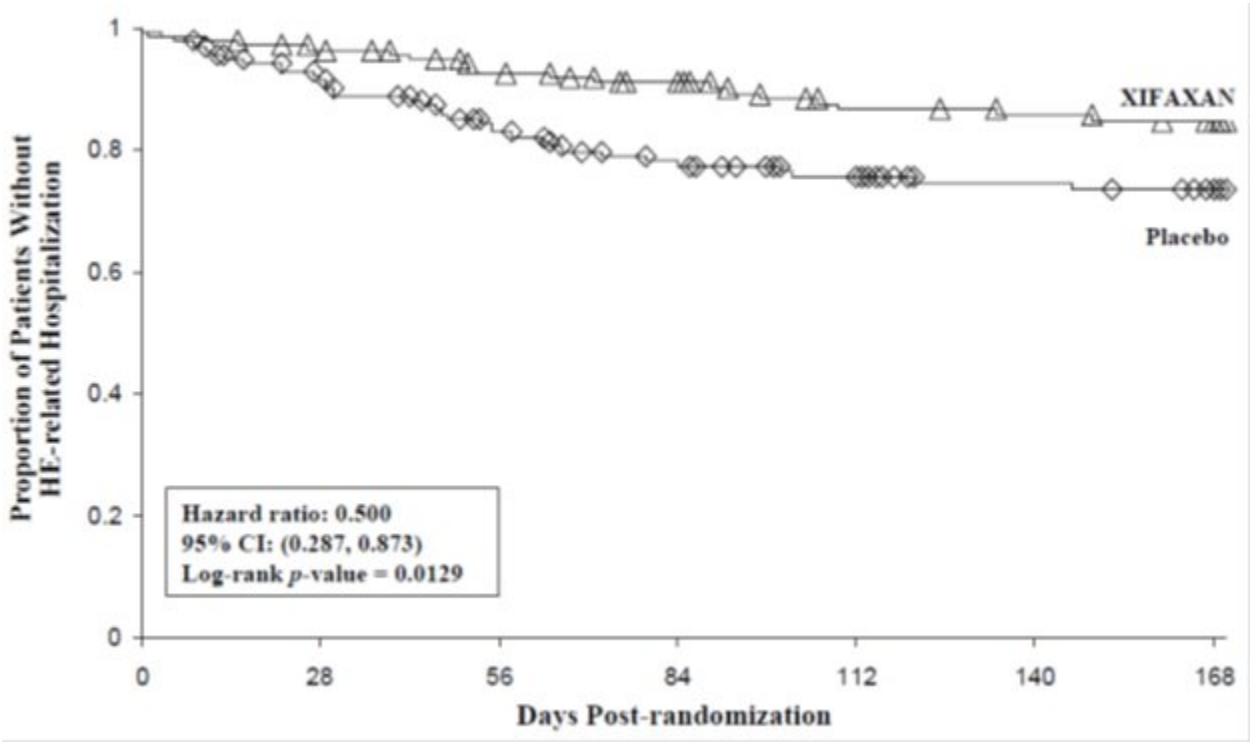


Figure 2 Kaplan-Meier Event-Free Curves1 in Pivotal HE Study (Time to First HE-Related Hospitalization in HE Study up to 6 Months of Treatment, Day 170) (ITT Population)

Note: Open diamonds and open triangles represent censored subjects.

[1]Event-free refers to non-occurrence HE-related hospitalization.

14.3 Irritable Bowel Syndrome with Diarrhea

The efficacy of XIFAXAN for the treatment of IBS-D was established in 3 randomized, multi-center, double-blind, placebo-controlled trials in adult patients.

Trials 1 and 2 – Design

The first two trials, Trials 1 and 2 were of identical design. In these trials, a total of 1258 patients meeting Rome II criteria for IBS* were randomized to receive XIFAXAN 550 mg three times a day (n=624) or placebo (n=634) for 14 days and then followed for a 10-week treatment-free period. The Rome II criteria further categorizes IBS patients into 3 subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), or alternating IBS (bowel habits alternating between diarrhea and constipation). Patients with both IBS-D and alternating IBS were included in Trials 1 and 2. XIFAXAN is recommended for use in patients with IBS-D.

*Rome II Criteria: *At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:* 1. Relieved with defecation; *and/or* 2. Onset associated with a change in frequency of stool; *and/or 3.* Onset associated with a change in form (appearance) of stool.

Symptoms that Cumulatively Support the Diagnosis of Irritable Bowel Syndrome:

– Abnormal stool frequency (for research purposes “abnormal” may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week); Abnormal stool form (lumpy/hard or loose/watery stool); Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); Passage of mucus; Bloating or feeling of abdominal distension.

Trial 3 - Design

Trial 3 evaluated repeat treatment in adults with IBS-D meeting Rome III criteria** for up to 46 weeks. A total of 2579 were enrolled to receive open-label XIFAXAN for 14 days. Of 2438 evaluable patients, 1074 (44%) responded to initial treatment and were evaluated over 22 weeks for continued response or recurrence of IBS-symptoms. A total of 636 patients had symptom recurrence and were randomized into the double-blind phase of the study. These patients were scheduled to receive XIFAXAN 550 mg three times a day (n=328) or placebo (n=308) for two additional 14-day repeat treatments courses separated by 10 weeks. See Figure 3.

Figure 3: Trial 3 Study Design

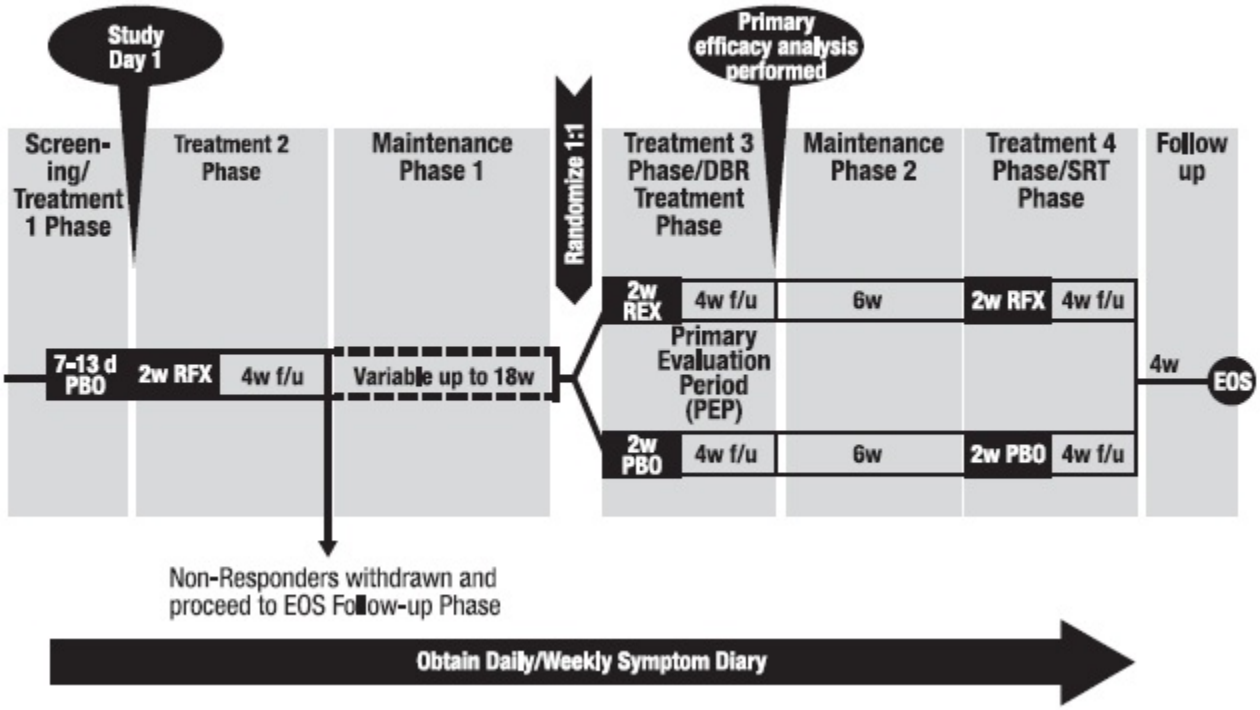


Figure 3 Trial 3 Study Design

The IBS-D population from the three studies had mean age of 47 (range: 18 to 88) years of which approximately 11% of patients were ≥65 years old, 72% were female and 88% were White.

**Rome III Criteria: Recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain) at least 3 days/month in last 3 months associated with *two or more* of the following: 1. Improvement with defecation; 2. Onset associated with a change in frequency of stool; 3. Onset associated with a change in form (appearance) of stool.

Trials 1 and 2 - Results

Trials 1 and 2 included 1258 IBS-D patients (309 XIFAXAN, 314 placebo); (315 XIFAXAN, 320 placebo). The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment. Adequate relief was defined as a response of "yes" to the following weekly Subject Global Assessment (SGA) question: *"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]."*

Adequate relief of IBS symptoms was experienced by more patients receiving XIFAXAN than those receiving placebo during the month following 2 weeks of treatment (SGA-IBS Weekly Results: 41% vs. 31%, p=0.0125; 41% vs. 32%, p=0.0263 (See Table 6).

Table 6. Adequate Relief of IBS Symptoms During the Month Following Two Weeks of Treatment

	Trial 1			Trial 2		
Endpoint	**XIFAXAN n=309 n (%)**	**Placebo n=314 n (%)**	**Treatment Difference (95% CI[1])**	**XIFAXAN n=315 n (%)**	**Placebo n=320 n (%)**	**Treatment Difference (95% CI[1])**
Adequate Relief of IBS Symptoms[2]	126 (41)	98 (31)	10% (2.1%, 17.1%)	128 (41)	103 (32)	8% (1.0%, 15.9%)

1. Confidence Interval
2. The p-value for the primary endpoint for Trial 1 and for Trial 2 was <0.05.

The trials examined a composite endpoint which defined responders by IBS-related abdominal pain *and* stool consistency measures. Patients were monthly responders if they met both of the following criteria:

- experienced a ≥30% decrease from baseline in abdominal pain for ≥2 weeks during the month following 2 weeks of treatment
- had a weekly mean stool consistency score <4 (loose stool) for ≥2 weeks during the month following 2 weeks of treatment

More patients receiving XIFAXAN were monthly responders for abdominal pain *and* stool consistency in Trials 1 and 2. (see Table 7).

Table 7. Efficacy Responder Rates in Trial 1 and 2 During the Month Following Two Weeks of Treatment

	Trial 1			Trial 2		
Endpoint	**XIFAXAN n=309 n (%)**	**Placebo n=314 n (%)**	**Treatment Difference (95% CI[1])**	**XIFAXAN n=315 n (%)**	**Placebo n=320 n (%)**	**Treatment Difference (95% CI[1])**
Abdominal Pain and Stool Consistency Responders[2]	144 (47)	121 (39)	8% (0.3%, 15.9%)	147 (47)	116 (36)	11% (2.7%, 18.0%)
Abdominal Pain Responders	159 (51)	132 (42)	9% (1.8%, 17.5%)	165 (52)	138 (43)	9% (1.5%, 17.0%)
Stool Consistency Responders	244 (79)	212 (68)	11% (4.4%, 18.2%)	233 (74)	206 (64)	10% (2.3%, 16.7%)

1. Confidence Interval
2. The p-value for the composite endpoint for Trial 1 and 2 was <0.05 and <0.01, respectively.

Trial 3 - Results

In TARGET 3, 2579 patients were scheduled to receive an initial 14-day course of open-label XIFAXAN followed by 4 weeks of treatment-free follow-up. At the end of the follow-up period, patients were assessed for response to treatment. Patients were considered a responder if they achieved both of the following:

- ≥30% improvement from baseline in the weekly average abdominal pain score based on the daily question: *"In regards to your specific IBS symptoms of abdominal pain, on a scale of 0-10, what was your worst IBS-related abdominal pain over the last 24 hours? 'Zero' means you have no pain at all; 'Ten' means the worst possible pain you can imagine".*
- at least a 50% reduction in the number of days in a week with a daily stool consistency of Bristol Stool Scale type 6 or 7 compared with baseline where 6=fluffy pieces with ragged edges, a mushy stool; 7=watery stool, no solid pieces; entirely liquid.

Responders were then followed for recurrence of their IBS-related symptoms of abdominal pain *or* mushy/watery stool consistency for up to 20 treatment-free weeks.

When patients experienced recurrence of their symptoms of abdominal pain *or* mushy/watery stool consistency for 3 weeks of a rolling 4-week period, they were randomized into the double-blind, placebo-controlled repeat treatment phase. Of 1074 patients who responded to open-label XIFAXAN, 382 experienced a period of symptom inactivity or decrease that did not require repeat treatment by the time they discontinued, including patients who completed the 22 weeks after initial treatment with XIFAXAN. See Figure 3.

Overall, 1257 of 2579 patients (49%) were nonresponders in the open-label phase and per the study protocol were withdrawn from the study. Other reasons for discontinuation include: patient request (5%), patient lost to follow-up (4%), adverse reaction (3%), and other (0.8%).

There were 1074 (44%) of 2438 evaluable patients who responded to initial treatment with improvement in abdominal pain *and* stool consistency. The response rate for each IBS symptom during the open-label phase of Trial 3 is similar to the rates seen in Trials 1 and 2 (see Table 7). A total of 636 patients subsequently had sign and symptom recurrence and were randomized to the repeat treatment phase. The median time to recurrence for patients who experienced initial response during the open-label phase with XIFAXAN was 10 weeks (range 6 to 24 weeks).

The XIFAXAN and placebo treatment groups had similar baseline IBS symptom scores at the time of recurrence and randomization to the double-blind phase, but symptom scores were less severe than at study entry into the open-label phase.

Patients were deemed to have recurrent signs and symptoms by the following criteria: a return of abdominal pain or lack of stool consistency for at least 3 weeks during a 4-week follow-up period. The primary endpoint in the double-blind, placebo-controlled portion of the trial was the proportion of patients who were responders to repeat treatment in both IBS-related abdominal pain *and* stool consistency as defined above during the 4 weeks following the first repeat treatment with XIFAXAN. The primary analysis was performed using the worst case analysis method where patients with <4 days of diary entries in a given week are considered as non-responders for that week.

More patients receiving XIFAXAN were monthly responders for abdominal pain *and* stool consistency in the primary analysis in Trial 3 (see Table 8).

Table 8. Efficacy Responder Rates in Trial 3 in a Given Week for at Least 2 Weeks During Weeks 3 to 6 of the Double-Blind, First Repeat Treatment Phase

	Placebo (n=308) n (%)	XIFAXAN (n=328) n (%)	Treatment Difference (95% CI[1])
Combined Responder[2]: Abdominal Pain and Stool Consistency Responders[3]	97 (31)	125 (38)	7% (0.9%, 16.9%)
Abdominal Pain Responders (*≥30% reduction in abdominal pain)*	130 (42)	166 (51)	9% (1.6%, 17.0%)
Stool Consistency Responders (*≥50% reduction from baseline in days/week with loose or watery stools)*	154 (50)	170 (52)	2% (-4.7%, 11.0%)

1. Confidence Intervals were derived based on CMH test adjusting for center and patients' time to recurrence during maintenance phase.
2. Primary endpoint
3. Subjects were IBS-related abdominal pain and stool consistency responders if they were both weekly IBS-related abdominal pain responders and weekly stool consistency responders in a given week for at least 2 weeks during Weeks 3 to 6 in the double-blind first repeat treatment phase. Weekly responder in IBS-related abdominal pain was defined as a 30% or greater improvement from baseline in the weekly average abdominal pain score. Weekly responder in stool consistency was defined as a 50% or greater reduction in the number of days in a week with stool consistency of type 6 or 7 compared with baseline. The p-value for this composite endpoint was <0.05.

Thirty six of 308 (11.7%) of placebo patients and 56 of 328 (17.1%) of XIFAXAN-treated patients responded to the first repeat treatment and did not have recurrence of signs and symptoms through the treatment-free follow-up period (10 weeks after first repeat treatment). The response rate difference was 5.4% with 95% confidence interval (1.2% to 11.6%).

15 REFERENCES

- Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard Ninth Edition. CLSI document M07-A9. Wayne, PA: Clinical and Laboratory Standards Institute, 2012.
- Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard Eighth Edition. CLSI document M11-A8. Wayne, PA: Clinical and Laboratory Standards Institute, 2012.
- Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement. CLSI document M100-S2. Wayne, PA: Clinical and Laboratory Standards Institute, 2014.

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 presentation:

- NDC 65649-301-03, bottles of 30 tablets

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
- NDC 65649-303-04, carton of 42 tablets, Unit Dose

Storage

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

17 PATIENT COUNSELING INFORMATION

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)]*.

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)]*.

Administration with Food

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

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.

Severe Hepatic Impairment

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

Manufactured for:

Salix Pharmaceuticals, Inc.

Raleigh, NC 27615

By:

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Web site: www.Salix.com

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Appendix II Commonly Used Medications, with Antimuscarinic Effects

Commonly Used Medications With Antimuscarinic Effects♦						
Antibiotics	Antihistamines	Cardiovascular	CNS	GI	Immunosuppressants	Respiratory
Ampicillin	Diphenhydramine	Captopril	Alprazolam	Atropine	Azathioprine	Ipratropium
Piperacillin	Hydroxyzine	Digoxin	Chlordiazepoxide	Cimetidine	Cyclosporine	Theophylline
Cefalothin		Diltiazem	Diazepam	Ranitidine	Dexamethasone	Tiotropium
Cefoxitin		Furosemide	Flurazepam		Hydrocortisone	
Clindamycin		Hydrochlorothiazide	Oxazepam		Prednisolone	
Gentamicin		Hydralazine	Codeine			
Tobramycin		Methyldopa	Oxycodone			
Vancomycin		Nifedipine	Tricyclic Antidepressants			
		Triamterene	Phenelzine			
		Warfarin	Phenobarbital			
			Chlorpromazine			
			Olanzapine			
			Clozapine			

CNS=central nervous system; GI= gastrointestinal

♦ Adapted from Tune et al (1992) & Tune (2001)
Source: Antimuscarinics
Department of Pharmacology. Tulane University SOM