Clinical Study Protocol with Amendment 01

A Randomized, Double-Blind, Placebo-Controlled, Parallel Design, Multicenter, Bioequivalence Study with Clinical Endpoint Comparing Rifaximin 200-mg Tablets with Xifaxan® 200-mg Tablets in the Treatment of Travelers' Diarrhea

Study Number ACTA/RIFX/2015

NCT02498418

Protocol with Amendment 01 Approval Date: 27 October 2015

Study Protocol

Version 2 – 27 October 2015

Amendment 1

A Randomized, Double-Blind, Placebo-Controlled, Parallel Design, Multicenter, Bioequivalence Study with Clinical Endpoint Comparing Rifaximin 200-mg Tablets with Xifaxan® 200-mg Tablets in the Treatment of Travelers' Diarrhea

Study Number:	**ACTA/RIFX/2015**
Study Phase:	Phase III
Investigational Product:	Rifaximin 200-mg Tablets
Indication:	Travelers' Diarrhea
Sponsor:	Actavis Morris Corporate Center III 400 Interpace Parkway Parsippany, NJ 07054 [redacted]

	Version Number	Version Date
Original Protocol	1.0	21 September 2015
Amendment 1	2.0	27 October 2015

Compliance Statement: This study will be conducted in accordance with the clinical research guidelines established by the US Code of Federal Regulations (CFR) (Title 21, Parts 50 [including Subpart D], 54, 56 and 312), and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP). Study documents will be maintained in accordance with applicable regulations.

Confidential: The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of Actavis or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation, unless such persons are bound by a confidentiality agreement with Actavis or its subsidiaries.

Investigator Signature Page

I have carefully read and understand the foregoing protocol ACTA/RIFX/2015 and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the Health Insurance Portability and Accountability Act (HIPAA- in countries where applicable) and/or with country-specific local regulatory guidelines. I will attempt to complete the study within the time designated.

I will ensure that the rights, safety, and welfare of patients under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide access to the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all patient information (source documents, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with FDA regulations.

I will not enroll any patients into this protocol until FDA approval (where applicable) or country competent authority approval, Local Ethics Committee (LEC)/Institutional Review Board (IRB) approval and Sponsor approval are obtained.

Investigator

_____ _____

Name, Function: Signature and Date
Institution:

Sponsor's Representatives

[redacted] Date

Actavis Inc

CRO Representatives

[redacted] Date

[redacted] Date

[redacted] Date

Lead Biostatistician

[redacted] Date

Protocol Synopsis

Sponsor: Actavis	**Name of Medical Product:** Rifaximin	**Active Ingredient:** Rifaximin
Study Sites: This will be a multicenter, multinational study.		
Study Duration: Treatment duration for a subject is 3 days. The duration for participation in the study for a subject could be up to 7 days		**Study Phase:** Phase III
Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Design, Multicenter, Bioequivalence Study with Clinical Endpoint Comparing Rifaximin 200-mg Tablets with Xifaxan® 200-mg Tablets in the Treatment of Travelers' Diarrhea		
Study objectives: The **primary objectives are:** (i) Bioequivalence of rifaximin 200-mg tablets (the test product) and Xifaxan® 200-mg tablets (the reference product) with respect to the clinical cure rates on Study Day 5 when administered 3 times a day (TID) for 3 days in subjects with Travelers' Diarrhea (TD). Clinical cure is defined as either of the following: ➢ 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. In addition, clinical deterioration by Study Day 5 or failure to achieve formed stool in ≤ 3 days is a clinical failure. (ii) Superiority of test and reference products over placebo with respect to the clinical cure rates on Study Day 5, in the treatment of TD, using the mITT population with LOCF. The **secondary objectives** of this study are the following: • To compare "Time to last unformed stool" (TLUS) observed for rifaximin 200-mg tablets and Xifaxan® 200-mg tablets on test of cure (TOC) visit (Study Day 5, 6 or 7). TLUS is defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed. • To compare the microbiological cure rate of rifaximin 200-mg tablets and Xifaxan® 200-mg tablets on test of cure (TOC) visit (Study Day 5, 6 or 7). Subjects are considered to have achieved microbiological cure if the pathogen identified at Visit 1 is no longer found in the stool at the TOC visit. Microbiological cure rate will be a supportive evidence of similarity between the test product and the reference product treatment arms and not considered as evidence of clinical bioequivalence.		
Methodology: This is a randomized, double-blind, placebo controlled, parallel design, multicenter, multinational bioequivalence study. Subjects will be adult, non-indigenous travelers with naturally acquired acute diarrhea. Eligible subjects must have at least 3 episodes of unformed stools recorded within the 24 hours immediately preceding randomization and at least one of the following signs and symptoms of enteric infection: abdominal pain or cramps, nausea, vomiting, fecal urgency, excessive gas/flatulence, or tenesmus. There will be 2 on-site study visits and 1 telephone visit (on Day 3, after taking about 5 doses of study medication). At the first visit, subjects will be screened and eligible subjects will be randomized [redacted] to receive rifaximin 200-mg tablets, Xifaxan® 200-mg tablets, or placebo tablets, TID for 3 days, beginning not more than 72 hours after the onset of diarrhea. The first dose of study drug should be preferably administered under the supervision of an unblinded dispenser/unblinded study staff member at the first study visit. For the second study visit, the study staff will contact the subject by telephone. The third visit is the TOC visit, which will occur 24 to 72 hours after the last dose of study drug. For 5 days		

Sponsor:	Name of Medical Product:	Active Ingredient:
Actavis	Rifaximin	Rifaximin

after randomization/first dose, subjects will record dosing, stool information (date, time, consistency) and enteric symptoms in a daily Diary. Stool samples will be collected pre-treatment (screening) and post-treatment (TOC) to be cultured for pathogenic organisms and microbiological cure rates. If the stool sample collection is not possible at visit 3, a rectal swab will be collected. Adverse events (AEs), concomitant medication details and safety laboratory samples will be collected at Visit 1 and Visit 3. AEs and concomitant medication details will also be obtained during Visit 2.

Number of Subjects (Planned): Approximately 618 [redacted] will be randomized [redacted] for test vs. reference vs. placebo [redacted] assuming that the overall dropout rate from the randomized population to mITT population is about 15%.

Diagnosis and Inclusion Criteria:

Subjects must meet all of the following inclusion criteria:

1. Adult male or nonpregnant female aged ≥ 18 years non-indigenous travelers (e.g., visiting students/faculty or international tourists) affected by naturally acquired acute diarrhea. Diarrhea is defined as the passage of at least three episodes of unformed stools in a 24-hour period. Stools are classified as formed (retains shape), soft (assumes shape of container), or watery (can be poured). When using this classification, both soft and watery stools are unformed and abnormal.
2. At least 3 episodes of unformed stools recorded within the 24 hours immediately preceding randomization (screening and randomization should occur as closely as possible on the same day, i.e. Day 1).
3. At least one of the following signs and symptoms of enteric infection:
    a. abdominal pain or cramps
    b. nausea
    c. vomiting
    d. fecal urgency
    e. excessive gas/flatulence
    f. tenesmus
4. Females of child bearing potential (WOCBP*) must not be pregnant or lactating at baseline visit (as documented by a negative urine pregnancy test with a minimum sensitivity of 25 IU/L or equivalent units of beta-human chorionic gonadotropin (Beta-HCG) at screening and urine pregnancy at baseline. **All female subjects will be considered to be of childbearing potential unless they are postmenopausal. WOCBP are defined as sexually mature women without prior hysterectomy, or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for the past 12 or more months are still considered to be of childbearing potential, if the amenorrhea is possibly due to other causes, including prior chemotherapy, antiestrogens, or ovarian suppression. Postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or women who have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy with surgery at least 4 weeks prior to randomization) are not considered WOCBP. Subjects who have undergone tubal ligation are NOT considered as surgically sterile*.
5. Female subjects of childbearing potential who are sexually active with males, must be willing to use an acceptable form of birth control from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (Medroxyprogesterone acetate- stabilized for at least 3 months); vaginal contraceptive; contraceptive implant; double barrier methods (e.g. condom and spermicide); Nuvaring vaginal hormonal birth control, intrauterine device (IUD), or abstinence with a second method of birth control should the subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control. Otherwise, they are not required to use a birth control method if they are in a same sex relationship.
6. All male subjects who are sexually active with females, must agree to use accepted methods of

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Actavis	Rifaximin	Rifaximin

birth control with their partners, from the day of the first dose administration (to 7 days after the last administration of study drug). Please see acceptable forms for "Female" birth control above. Abstinence is an acceptable method of birth control for males. Otherwise, they are not required to use a birth control method if they are in a same sex relationship.

7. Subject must be willing and able to comply with study procedures for the duration of the study.
8. Study subjects must have provided Local Ethics Committee (LEC)/ Institutional Review Board (IRB) approved written informed consent using the latest version of the LEC/IRB informed consent form. In addition, study subjects must sign a Health Insurance Portability and Accountability Act (HIPAA) authorization, if applicable.
9. Subject has to be literate and able to sign the informed consent form (ICF) and complete the Diary.

Exclusion Criteria:

Potential subjects will be excluded if any of the following exclusion criteria are present:

1. Is pregnant, breast feeding, or planning a pregnancy.
2. Immediately prior to randomization, acute diarrhea for > 72 hours.
3. Has:
    a. fever (≥ 100 °F or ≥ 37.8 °C), or
    b. hematochezia (blood in stool), or
    c. clinical findings suggesting moderate or severe dehydration.
4. Has 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.
5. Administration of any of the following:
    a. any antimicrobial agents with an expected activity against enteric bacterial pathogens within 7 days preceding randomization
    b. more than two doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents within 8 hours preceding randomization
    c. any nonsteroidal anti-inflammatory drug or fever-reducing agent, such as aspirin or ibuprofen, which can cause GI bleeding within 8 hours preceding randomization. Acetaminophen or paracetamol is acceptable.
    d. Use of opioids (in any form) within 48 hours preceding randomization
6. History or presence of allergic response to rifaximin or related drugs.
7. People who have lived in or stayed in the country where they acquired travelers' diarrhea for more than 6 months.
8. Has a history of lactose or gluten intolerance.
9. Consumed more than 2 alcoholic drinks within 12 hours before screening. Alcohol consumption is not allowed during the study
10. Has a current or recent history (within 12 months of screening) of drug or alcohol abuse.
11. A positive urine drug screen test in the absence of therapeutic use will exclude the subject from participating in the study at the investigator's discretion.
12. Family members of the investigator and the independent dispenser/unblinded staff member, nor site staff of this study
13. Subject currently enrolled in any other clinical investigation or who has participated in any clinical investigation within 30 days prior to starting this study.

Test Product, Dose, and Mode of Administration:

Rifaximin 200-mg film-coated oral tablets. Each subject will receive 1 tablet TID (morning, noon and evening) for 3 days, which is the recommended dosing regimen for Xifaxan®

Reference Therapy, Dose, and Mode of Administration:

Xifaxan® 200-mg film-coated oral tablets; 1 tablet TID for 3 days (morning, noon and evening).

Placebo, Dose, and Mode of Administration:

Placebo film-coated oral tablets; 1 tablet TID for 3 days (morning, noon and evening).

Sponsor: Actavis	Name of Medical Product: Rifaximin	Active Ingredient: Rifaximin

Endpoints for Evaluation:

Primary efficacy endpoint

The primary efficacy endpoint is clinical cure rate on TOC Visit (Study Day 5, 6 or 7).

Clinical cure is defined as either of the following:

- 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.

In addition, clinical deterioration by Study Day 5 or failure to achieve formed stool in ≤ 3 days is a clinical failure.

Secondary efficacy endpoints

Secondary efficacy endpoints are the following:

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

  Mathematically, TLUS will be calculated as follows:
  TLUS (hours) = date/time of last unformed stool – date/time of first dose
- Microbiological cure rate. Subjects are considered to have achieved microbiological cure if the pathogen identified at Visit 1 is no longer found in the stool at the TOC visit. Microbiological cure rate will be a supportive evidence of similarity between the test product and the reference product treatment arms and not considered as evidence of clinical bioequivalence.

Safety

All adverse events (AEs) and treatment-emergent AEs (TEAEs) reported during the study will be summarized/reviewed in order to assess safety.

Statistical Methods:

The following 3 analysis populations will be defined for this study:

- Safety analysis set: All randomized subjects who receive at least one dose of study drug. The Safety Analysis Set will be used for all analyses of safety, tolerability, and background characteristics.
- mITT analysis set: [redacted]
- Per protocol (PP) analysis set: [redacted]

[redacted].

Note: Visit 2 data i.e. data from the telephone follow-up call on Day 3, after taking about 5 doses of study medication, may be used for applying LOCF for mITT population for the cases where TOC data is missing.

Two sets of null hypotheses will be used for the primary efficacy endpoint to evaluate the clinical

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bioequivalence between test product and reference products with respect to the clinical cure rate using PP population. The 90% confidence interval (CI) for the difference (test – reference) in clinical cure rates will be calculated using Z-test with Yates' correction. If the lower and upper CIs are within the range of [-0.20, +0.20], it can be claimed that the test and the reference products are clinically bioequivalent. Otherwise, the two products will be considered as clinically not bioequivalent. The other null hypothesis will evaluate the differences between each active arm versus placebo using a two-sided Z-test for proportion with Yates correction, each at 0.05 significance level, for testing superiority of each active arm compared to the placebo. This evaluation will be performed on the mITT analysis set using LOCF for missing data imputation, and would establish the sensitivity of the study.

No interim analysis is planned for this study.

The secondary efficacy endpoints, TLUS & Microbiological cure rate, will be tabulated by treatment group on the mITT and PP analysis sets with appropriate descriptive statistics. The comparisons (test vs placebo, reference vs placebo, test vs reference) will be conducted at the 0.05 significance level. All secondary efficacy analyses are considered supportive/confirmative.

All safety endpoints will be tabulated by treatment group on the safety analysis set without formal inferential statistics. AEs will be mapped using Medical Dictionary for Regulatory Activities (MedDRA, using the latest available version) with respect to the system organ class (SOC) and the preferred term. Change from baseline in clinical laboratory tests, vital signs, and physical examinations will be summarized by treatment group.

Additional summaries will include disposition, baseline characteristics and demographics.

Approximately 618 [redacted] will be randomized [redacted] for test vs. reference vs placebo. [redacted] The sample size for this study was based on Z-test for proportion with Yates correction for bioequivalence of test vs. reference and superiority of the efficacy of the test and reference products over a placebo. [redacted] To establish bioequivalence for the primary endpoint (proportion of subjects with "clinical cure" at study Day 5), the 90% CI of the test - reference difference between products must contained within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP population. As a parameter for determining adequate study sensitivity, the test and reference products should be statistically superior to placebo ($p<0.05$, two-sided) for the primary endpoint using the mITT study population with LOCF.

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Glossary of Abbreviations

Abbreviation	Definition
AE(s)	Adverse event(s)
ATC	Anatomical Therapeutic Chemical
CDC	Centers for Disease Control
CFR	Code of Federal Regulation
CI	Confidence interval
CRO	Contract research organization
eCRF	Electronic Case report form
ETEC	Enterotoxigenic *Escherichia coli*
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive Web Response System
LEC	Local Ethics Committee
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
N	Number of subjects
NDA	New Drug Application
O&P	Ova and parasites
OTC	Over-the-counter
PP	Per protocol
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Statistical analysis software
SE	Standard error
SOC	System organ class
SOP	Standard operating procedure
SQRT	Square root
TEAE	Treatment-emergent adverse event
TD	Travelers' diarrhea
TID	Three times per day
TLF	Tables, listings and figures
TLUS	Time to last unformed stool
TOC	Test of cure
US	United States

Abbreviation	Definition
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of child-bearing potential
WMA	World Medical Assembly

1. Introduction and Study Rationale

Travelers' diarrhea (TD) is the most common illness affecting travelers. Each year between 20%-50% of international travelers, an estimated 10 million persons, develop diarrhea (Centers for Disease Control [CDC] 2014). The onset of TD usually occurs within the first week of travel. Episodes of TD are typically benign and self-limited, lasting anywhere from 2 to 5 days. High-risk destinations for TD are the developing countries of Latin America, Africa, the Middle East, and Asia. Persons at particularly high-risk include young adults, immunosuppressed persons, persons with inflammatory-bowel disease or diabetes, and persons taking H-2 blockers or antacids. Attack rates are similar for men and women. The primary source of infection is ingestion of fecally contaminated food or water (CDC 2014). A variety of bacterial, viral, and parasitic organisms can cause TD, but bacterial pathogens (especially enterotoxigenic *Escherichia coli* [ETEC]) predominate.

Standard treatment typically consists of 3 components - fluid replacement, antibiotics, and antimotility agents. Fluid replacement is important to avoid dehydration. Antibiotics help shorten the disease duration (typically to one day), while antimotility agents may limit the frequency of loose stools.

Current antibiotic choices include fluoroquinolones, azithromycin, and rifaximin. Bactrim was widely used in the past, but due to widespread resistance among routine enteric pathogens, this medication is less useful now. Fluoroquinolones are frequently used, as they are readily available, easy to tolerate, and have activity against many of the common pathogens. However, resistance is growing, particularly among *Campylobacter jejuni isolates* in Southeast Asia, which increases the importance of alternative choices such as azithromycin and rifaximin.

Rifaximin (marketed as Xifaxan®) is primarily effective in treating ETEC-associated TD and less effective for treating Campylobacter-associated TD. This results in destination-based antibiotic recommendations from clinical practitioners, which is reflected in the choice of region for the current trial. This trial is designed to demonstrate that a generic formulation of rifaximin 200-mg tablets is clinically bioequivalent to Xifaxan® 200-mg tablets (Salix Pharmaceuticals, Inc.).

2. Study Objectives

The **primary objectives** are:

(i) Bioequivalence of rifaximin 200-mg tablets (the test product) and Xifaxan® 200 mg tablets (the reference product) with respect to the clinical cure rates on Study Day 5 when administered 3 times a day (TID) for 3 days in subjects with TD.

Clinical cure is defined as either of the following:

- 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.

In addition, clinical deterioration by Study Day 5 or failure to achieve formed stool in ≤ 3 days is a clinical failure.

(ii) Superiority of test and reference products over placebo with respect to the clinical cure rates on Study Day 5, in the treatment of TD, using the mITT population with LOCF.

The **secondary objectives** of this study are the following:

- To compare the time to last unformed stool (TLUS) observed for rifaximin 200-mg tablets and Xifaxan® 200-mg tablets on test-of-cure (TOC) visit (Study Day 5, 6 or 7). TLUS is defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed.
- To compare the microbiological cure rate of rifaximin 200-mg tablets and Xifaxan® 200-mg tablets on test-of-cure (TOC) visit (Study Day 5, 6 or 7). Subjects are considered to have achieved microbiological cure if the pathogen identified at Visit 1 is no longer found in the stool at the TOC visit. Microbiological cure rate will be a supportive evidence of similarity between the test product and the reference product treatment arms and not considered as evidence of clinical bioequivalence.

3. Investigational Plan

This is a randomized, double-blind, placebo-controlled, parallel design, multicenter, multinational bioequivalence study. Subjects will be adult, non-indigenous travelers with naturally acquired acute diarrhea. Eligible subjects must have at least 3 episodes of unformed stools recorded within the 24 hours immediately preceding randomization (screening and randomization should occur as closely as possible on the same day, i.e. Day 1) and at least one of the following signs and symptoms of enteric infection: abdominal pain or cramps, nausea, vomiting, fecal urgency, excessive gas/flatulence, or tenesmus. There will be 3 study visits: 2 visits on-site and 1 telephone visit (on Day 3 after taking about 5 doses of study medication). At the first visit, subjects will be screened and eligible subjects will be randomized [redacted] to receive Rifaximin 200-mg tablets, Xifaxan® 200-mg tablets, or placebo tablets, TID for 3 days, beginning not more than 72 hours after the onset of diarrhea. The first dose of study drug should be preferably administered under the supervision of an unblinded study staff member/independent dispenser at the first study visit. For the second visit, the study site will contact the subject by telephone to follow-up on Day 3, after taking about 5 doses of study medication. The third visit is the TOC visit, which will occur 24 to 72 hours after the last dose of study drug. For 5 days after randomization/first dose, subjects will record dosing, stool information (date, time, consistency) and enteric symptoms in a daily Diary. Stool samples will be collected pre-treatment (screening) and post-treatment (TOC) to be cultured for pathogenic organisms. If the stool sample collection is not possible at visit 3, a rectal swab will be collected. Adverse events (AEs), concomitant medication details and safety laboratory samples will be collected at Visit 1 and Visit 3. AEs and concomitant medication details will also be obtained during Visit 2.

Safety and efficacy assessments will be performed as noted in the Schedule of Procedures and Assessments (Section 6.1).

4. Selection of Study Population

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Be adult male or nonpregnant female aged ≥ 18 years non-indigenous travelers (e.g., visiting students/faculty or international tourists) affected by naturally acquired acute diarrhea. Diarrhea is defined as the passage of at least 3 episodes of unformed stools in a 24-hour period. Stools are classified as formed (retains shape), soft (assumes shape of container), or watery (can be poured). When using this classification, both soft and watery stools are unformed and abnormal.
2. Have at least 3 episodes of unformed stools recorded within the 24 hours immediately preceding randomization (screening and randomization should occur as closely as possible on the same day, i.e. Day 1).
3. Have at least one of the following signs and symptoms of enteric infection:
    a. abdominal pain or cramps
    b. nausea
    c. vomiting
    d. fecal urgency
    e. excessive gas/flatulence
    f. tenesmus
4. Females of child bearing potential (WOCBP*) must not be pregnant or lactating at baseline visit (as documented by a negative urine pregnancy test with a minimum sensitivity of 25 IU/L or equivalent units of beta-human chorionic gonadotropin (Beta-HCG) at screening and urine pregnancy at baseline. **All female subjects will be considered to be of childbearing potential unless they are postmenopausal. WOCBP are defined as sexually mature women without prior hysterectomy, or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for the past 12 or more months are still considered to be of childbearing potential, if the amenorrhea is possibly due to other causes, including prior chemotherapy, antiestrogens, or ovarian suppression. Postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or women who have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy with surgery at least 4 weeks prior to randomization) are not considered WOCBP. Subjects who have undergone tubal ligation are NOT considered as surgically sterile*.
5. Female subjects of childbearing potential who are sexually active with males, must be willing to use an acceptable form of birth control from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera®

(Medroxyprogesterone acetate- stabilized for at least 3 months); vaginal contraceptive; contraceptive implant; double barrier methods (e.g. condom and spermicide); Nuvaring vaginal hormonal birth control, intrauterine device (IUD), or abstinence with a second method of birth control should the subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control. Otherwise, they are not required to use a birth control method if they are in a same sex relationship.

6. All male subjects who are sexually active with females, must agree to use accepted methods of birth control with their partners, from the day of the first dose administration to 7 days after the last administration of study drug. Please see acceptable forms for "Female" birth control above. Abstinence is an acceptable method of birth control for males. Otherwise, they are not required to use a birth control method if they are in a same sex relationship.
7. Subject must be willing and able to comply with study procedures for the duration of the study.
8. Study subjects must have provided Local Ethics Committee (LEC)/ Institutional Review Board (IRB) approved written informed consent using the latest version of the LEC/IRB informed consent form. In addition, study subjects must sign a Health Insurance Portability and Accountability Act (HIPAA) authorization, if applicable.
9. Subject has to be literate and able to sign the informed consent form (ICF) and complete the Diary

4.2 Exclusion Criteria

Potential study subjects will be excluded if any of the following exclusion criteria are present:

1. Is pregnant, breast feeding, or planning a pregnancy.
2. Immediately prior to randomization has acute diarrhea for > 72 hours.
3. Has :
    a. fever (≥ 100 °F or ≥ 37.8 °C), or
    b. hematochezia (blood in stool), or
    c. clinical findings suggesting moderate or severe dehydration.
4. Has 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.
5. Administration of any of the following:
    a. any antimicrobial agents with an expected activity against enteric bacterial pathogens within 7 days preceding randomization.

b. more than two doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents preceding randomization.

c. any nonsteroidal anti-inflammatory drug or fever-reducing agent, such as aspirin or ibuprofen, which can cause GI bleeding within 8 hours preceding randomization. Acetaminophen or paracetamol is acceptable.

d. Use of opioids (in any form) within 48 hours preceding randomization.

6. Has a history or presence of allergic response to rifaximin or related drugs.
7. People who have lived in or stayed in the country where they acquired travelers' diarrhea for more than 6 months.
8. Has a history of lactose or gluten intolerance.
9. Consumed more than 2 alcoholic drinks within 12 hours before screening. Alcohol consumption is not allowed during the study.
10. Has a current or recent history (within 12 months of screening) of drug or alcohol abuse.
11. A positive urine drug screen test in the absence of therapeutic use will exclude the subject from participating in the study at the investigator's discretion.
12. Family members of the investigator and the independent dispenser/unblinded staff member, nor site staff of this study.
13. Subject currently enrolled in any other clinical investigation or who has participated in any clinical investigation within 30 days prior to starting this study.

4.3 Restrictions

The following are not allowed in this study:

- Any antimicrobial agents with an expected activity against enteric bacterial pathogens within 7 days preceding randomization and during the study.
- More than two doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents preceding randomization and during the study.
- Use of any drug such as aspirin or ibuprofen (Advil), which can cause GI bleeding within 8 hours preceding randomization and during the study. Note: Acetaminophen (Tylenol) or paracetamol is acceptable for use during the study.
- Opioids (in any form) within 48 hours preceding randomization and during the study.
- Alcohol or probiotics consumption

4.4 Withdrawals and Replacement of Subjects

Subjects may be discontinued from study treatment and assessments at any time. Subjects are also free to discontinue their participation in the study at any time, without prejudice to further treatment.

Study completion or discontinuation and the reason for discontinuation will be documented. Possible reasons for a subject discontinuing participation in the study are:

- AE(s) that endanger the health of subjects, making it ethically unacceptable to continue
- Deterioration of the subject's clinical condition(s) that requires appropriate therapy/treatment during the study period
- Lack of efficacy
- Withdrawal of consent
- Lost to follow up
- Death.

In case of an AE, the subject is to be followed up until resolution of the AE. Subjects who discontinue prematurely from the study will not be replaced. Investigational products and study materials should be returned by the subject.

5. Treatments

5.1 Description of Treatment(s)

The treatments used in this study are the following:

- Rifaximin 200-mg tablets (test product) manufactured by Actavis Laboratories FL, Inc.
- Xifaxan® 200-mg tablets (reference product) of Salix Pharmaceuticals, Inc. (Valeant Pharmaceuticals group of company)
- Placebo tablets manufactured by Actavis Laboratories FL, Inc.

Rifaximin is marketed under the tradename Xifaxan® (Salix Pharmaceuticals, Inc, recently acquired by Valeant Pharmaceuticals). The investigational drug evaluated in this study is generic rifaximin.

5.2 Selection and Timing of Dose for Each Subject

Each subject will receive the same dosing regimen of 1 tablet TID (morning, noon and evening) for 3 days, which is the recommended dosing regimen for Xifaxan®.

Subjects who take 3 doses of study drug on Day 1 (i.e., those randomized early in the day on Day 1) will complete study drug on Day 3; other subjects will receive the last dose of study drug on Day 4.

5.3 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly allocated [redacted] to treatment groups to receive the Test product or the Reference Product or the Placebo control, respectively. The randomization schedule for this study will be generated by a third party vendor of the CRO such that a non-study-assigned independent expert will allocate the subjects to one of the three treatment arms using a computer generated automated process i.e. Interactive Web Response System (IWRS).

[redacted]

Study sites should have an unblinded dispenser/unblinded study staff member assigned to maintain blinding throughout the study. Subject must return the study treatment bottle with original carton to the unblinded study staff member.

5.4 Unblinding

In case of emergency, if the detail of study drug is required for management of emergency as per the opinion of investigator, investigator can unblind the product that is received by the patient during the study. In case of non- emergency condition that requires study drug information for management of condition as per investigator's opinion, investigator should obtain sponsor or medical monitor approval in writing prior to breaking of the blind. [redacted] It is recommended that all attempts should be made to maintain the blind of the study. However, in case the unblinding is performed, the reason for breaking the blind must be clearly documented in the source documentation and electronic case report form (eCRF) and the patient must be discontinued from the study.

5.5 Packaging and Labeling

Packaging and labeling will be carried out in accordance with the requirements of the Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements, sponsor approved standard operating procedures (SOPs) and all applicable country specific laws. A detailed packaging and labelling plan will be put in place with country specific requirements.

Final labeling and packaging of the products will be performed by

[redacted]
Actavis Laboratories UT, Inc.
[redacted]

in accordance with their SOPs and international requirements. Product labels comply with United States (US) regulatory requirements and languages, and in the case of other participant countries will comply with applicable local regulatory requirements.

5.6 Retention Sample Selection, Storage and Accountability

Retention of Reserve Samples

For every study product shipment received at the Investigator site, the Investigator (or designee) will randomly select at least one block of study product for retention, unless otherwise instructed by the Sponsor and/or CRO. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement, and the same will be documented. [redacted]
The number of each block kept for retention will be noted on the drug accountability form as

a retention sample, in addition to the retention sample log. These retention samples should be stored under the appropriate storage conditions for a minimum of 5 years following the application approval or, if not approved, at least 5 years after the completion of the study. Retention samples should not be returned to the sponsor at any time. The retention samples can be shipped to a third party storage facility. A detailed investigational product plan will be provided to the study site.

Product storage and dispensation

All study material, together with necessary documentation, will be supplied to the study site before starting the trial. The study site will acknowledge receipt of all study material in IWRS.

All supplies will be maintained under adequate security by the clinical investigator or unblinded study staff member/independent dispenser, who will be responsible for all supplies.

The study drugs are to be stored at 20° to 25°C (68° to 77°F) with excursions permitted from 15° to 30°C (59° to 86°F).

The study drugs are to be dispensed only under the restricted conditions defined in the present protocol.

Any test materials remaining at the end of the study will be returned to the designated drug depots or destroyed in accordance with the guidelines provided by Sponsor. Before destruction, detailed product accountability has to be performed. An official document on what has been destroyed has to be issued and sent to the Sponsor/CRO.

Product accountability

Each center will be responsible for maintaining an accurate log and inventory of study material received and returned to the designated drug depot.

At the end of the study, it must be possible to reconcile delivery records with records of used and returned study treatments. An account of any discrepancies has to be provided.

The designated CRO will provide the framework for documenting study treatment accountability, without breaking the blind, throughout the study. CROs will assign unblinded CRAs to perform the drug accountability.

The investigator has to maintain an accurate written record of the shipment, retention, dispensing, and return of study treatments using a drug accountability form. An accurate record of the date and amount of study drug dispensed to each subject has to be available for inspection at any time. The designated CRO representatives will verify drug accountability during routine site monitoring visits without breaking the blind. The total drug accountability will also be performed at the completion of the trial.

At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused drug containers, drug labels, and a copy of the completed drug accountability form to the Sponsor/designee. Some sites may destroy medications locally at an appropriate time point, if previously agreed with the sponsor.

5.7 Treatment Compliance

Subject compliance will be primarily monitored by counting the study tablets dispensed (Visit 1) and returned (Visit 3) compared to diary entries. The medication dispensed and/or returned will be recorded by the independent dispenser/unblinded study staff member in the subject drug accountability log and eCRF. Subjects will be asked to return all original packaging and unused study drug at Visit 3. Compliance calculation will be based on number of tablets taken (as recorded in the study diary) vs number of tablets subjects are expected to take.

5.8 Concomitant Medications and Therapy

All concomitant medications and therapies used during the trial will be documented in the eCRF including name of the medication, date of administration and its duration, and indication for use.

Over-the-counter (OTC) anti-diarrheal medications, NSAIDs (with the exception of acetaminophen and paracetamol) and opioid analgesics are prohibited during the study. For further detail, please refer to Section 4.3 of the protocol. Use of prohibited concomitant medications will be considered a major protocol deviation and the subjects will be withdrawn from the study; and will be excluded from the per protocol (PP) analysis set.

6. Study Procedures

6.1 Schedule of Events

A schedule of study procedures is provided in Table 1.

Table 1 Schedule of Events

	Screening, Randomization and Treatment	Treatment			TOC
	Day 1	Day 2	Day 3[a]	Day 4[b]	5, 6 or 7[c]
Assessments	Visit 1		Visit 2		Visit 3
Informed consent, I/E criteria	X				
Demographic information	X				
Medical history	X				
Prior/concomitant medications	X		X		X
Physical examination	X				X
Vital signs	X				X
Stool sample for culture and O&P	X				X[f]
Hematology/chemistry panel	X				X
Urinalysis	X				X
Urine drug screen	X				
Pregnancy test (urine)[d]	X				X
Randomization	X				
Telephone call			X		
Study drug dosing	X	X	X	X	
Daily study diary completion[e]	X	X	X	X	X
Adverse events	X		X		X

TOC = test of cure; I/E = inclusion/exclusion; O & P = ova and parasites

[a] Visit 2 assessment should be done by telephone (after the subject has taken about 5 doses); the subject should be contacted by a member of the study team.

[b] If a subject takes 3 doses of study drug on Day 1, then study drug should be completed on Day 3, otherwise the final doses will be taken on Day 4.

[c] Visit 3 should occur 24 to 72 hours after the last dose of study drug. If a subject does not return for the scheduled TOC visit, a telephone call should be made and efficacy and safety data (same as Visit 2) should be collected for Visit 3.

[d] Female subjects of child-bearing potential only.

[e] Study drug diary completion will begin on Study Day 1 and end on last study visit. Diary completion includes recording of temperature if a subject feels feverish; (a thermometer should be provided to each subject by the site), date/time of study drug each dose; date, time and consistency of stool; as well as enteric symptoms described in protocol

[f] In case stool sample collection not possible at visit 3, a rectal swab will be collected.

6.2 Screening, Randomization and Treatment Visit

Visit 1/Day 1:

When a suitable candidate is identified, the investigator or designated healthcare professional will ask the subject about their willingness to be included in the clinical trial.

The subject is to be informed verbally and in writing about the nature, risks, benefits, and expectations of participating in the clinical trial and a copy of the subject informed consent form is to be given to the subject in the appropriate language. The subject informed consent form is to be signed by the subject and by the attending investigator/ designee, prior to proceeding with the screening activities. The subject number should be assigned at the time of starting the consent process.

The following observations/procedures are to be performed/checked:

- Check of inclusion/exclusion criteria
- Gender, age, race
- Complete medical history
- Brief physical examination including vital signs (body temperature, blood pressure, and pulse) and body weight and height
- Review of the use of previous/concomitant treatments for any other clinical condition(s)
- Stool sample for culture (at a minimum, pathogenic *E. coli*) and O&P (Ova and Parasites)
- Blood sample for hematology/chemistry panel
- Urine sample for urinalysis and urine drug screen
- Urine pregnancy test for WOCBP
- Review of AEs

Eligible subjects will be randomized and the first dose of study drug should be preferably administered under unblinded study staff/independent dispenser supervision at the clinic. Subjects should be suggested to start the first dose of the study drug only after providing the stool sample. [redacted] Subjects will be given a study drug diary, a thermometer and record the following for 5 days, beginning on Study Day 1:

- Date and time of each dose
- Date, time, and consistency of each stool
- Temperature (if feeling feverish)
- Enteric infection symptoms:
  - abdominal pain or cramps,
  - excessive gas/flatulence,
  - nausea,

- vomiting,
- fecal urgency,
- blood and/or mucus in the stool,
- tenesmus

Subjects will be observed for the occurrence of AEs after informed consent is signed.

6.3 Treatment

Days 2 to 4

Subjects are to take 1 study drug tablet TID (morning, noon and evening) for 3 consecutive days for a total of 9 doses. Subjects who take 3 doses of study drug on Day 1 (i.e., those randomized early in the day on Day 1) will complete study drug on Day 3; other subjects will receive the last dose of study drug on Day 4. Subject will complete study diary until last study visit day, beginning on Day 1. Subjects will record the following in the study diary:

6.4 Telephone Follow-Up

Visit 2/Telephone Visit (Day 3)

On study Day 3 (after about 5 doses), subjects should be contacted by a member of the study team to undergo a telephone follow-up. Subjects will be asked about their AEs, concomitant medications and general health as well as their diary entries (see Section 6.3).

6.5 Test of Cure

Visit 3 (Day 5, 6 or 7)

Visit 3 will be the TOC visit and should be scheduled 24 to 72 hours after the last dose of study drug (i.e., after taking about 9 doses during the duration of the study). The following procedures are to be performed/checked:

- Stool sample for culture and examination
- Blood sample for hematology/chemistry panel
- Urine pregnancy test for WOCBP
- Brief physical examination including vital signs (body temperature, blood pressure, and pulse) and body weight and height
- Review of the use of concomitant treatments for any other clinical condition(s)
- Review of AEs
- Study medication compliance
- Return of unused study medication.

Subjects are to complete the study diary from day 1 until last study visit day.

If the stool sample collection is not possible at Visit 3, a rectal swab will be collected.

Note: If a subject does not return for the scheduled TOC visit (Visit 3; 24 to 72 hours after last dose of study medicine) then a telephone call should be made by the site and all the efforts should be made to collect efficacy and safety data for Visit 3. This data should be entered in eCRF for Visit 3 records.

6.6 Unscheduled Visits and Early Discontinuation Visit

An Unscheduled Visit is allowed at any time, for any reason, if in the Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Investigator will determine whether additional visits are needed.

If a subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 3 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the subject will continue to take part in the study), then study procedures will be performed at the discretion of the investigator, with the exception of the collection of IMP and subject diaries from subjects.

If the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Investigator's discretion.

7. Efficacy and Safety Assessments

7.1 Methods of Assessment

All eligible subjects will be screened and randomized at Visit 1. The first dose of study drug should be preferably administered under the supervision of unblinded clinical staff/independent study dispenser at the clinic immediately after randomization. Subjects are provided with a study diary to record study drug doses; time and characteristics of each bowel movement; and enteric symptoms for 5 days.

7.2 Primary Efficacy Parameter

The primary efficacy endpoint will be clinical cure rate on TOC Visit (Study Day 5, 6 or 7).

Clinical cure is defined as either of the following:

- 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.

In addition, clinical deterioration by Study Day 5 or failure to achieve formed stool in ≤ 3 days is a clinical failure.

7.3 Secondary Efficacy Parameters

Secondary efficacy endpoints are the following:

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

   Mathematically, TLUS will be calculated as follows.

   TLUS (hours) = date/time of last unformed stool – date/time of first dose

2. Microbiological cure rate. Subjects are considered to have achieved microbiological cure if the pathogen identified at Visit 1 is no longer found in the stool at the TOC visit. Microbiological cure rate will be a supportive evidence of similarity between the test product and the reference product treatment arms and not considered as evidence of clinical bioequivalence.

7.4 Safety Parameters

Safety parameters will include the following:

1. Treatment emergent adverse events (TEAEs)
2. Subjects with the following TEAEs of special interest
    a. Fever
    b. Moderate or severe dehydration
    c. Hematochezia (blood in stool)
    d. Abdominal pain or cramps
    e. Nausea
    f. Vomiting
    g. Fecal urgency
    h. Excessive gas/flatulence
    i. Tenesmus
3. Changes in clinical laboratory tests, vital signs, and physical examinations from baseline

7.5 Adverse Events

All AEs that occur during the study after the subject has signed the informed consent are to be collected and reported on the eCRF, regardless of whether they are reported by the subject, observed by investigator/designee, or by any other means. All AEs are to be followed up till resolution or up to a maximum of 30 days from the date of occurrence.

As far as possible, each AE is described by:

- duration (start and end date)
- start/end of study medication
- severity grade (mild, moderate, severe)
- investigator causality (relationship to the study product)
- action(s) taken (concomitant medication, change of study medication etc.) including start and end of respective action
- concomitant diseases and respective medication in general
- outcome.

AE

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. 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.

TEAE

TEAEs are those AEs occurring after first dose of study drug through the TOC or as noted in completed study diary, whichever is later. TEAEs are also events that were present prior to the first dose of study drug, but increased in frequency or severity following initiation of study drug.

SAE

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

- results in death
- is life-threatening (Note: the term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically may cause death if it is more severe)
- requires subject hospitalization or prolongation of existing hospitalization (for the purpose of this study, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

or

- other medically important condition

Events that require intervention to prevent one or more of the outcomes listed in the definition above are also to be considered as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalization, or development of drug dependency or drug abuse.

However, medical judgment has to be exercised in deciding whether an event is serious in any other situations considered medically relevant.

The evaluation of the AE as serious or not-serious is made independently of any attribution of causality.

Events NOT considered to be SAEs are those that require:

- treatment, which is elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and does not worsen
- treatment on an emergency, outpatient basis for an event NOT fulfilling any of the definitions of serious given above and NOT resulting in hospital admission for the

purpose of this study, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay).

AE intensity

AE intensity determined by the clinical investigator on the basis of his/her direct observations or the subject's reporting:

- Mild: causes no limitation of usual activities; the subject may experience slight discomfort
- Moderate: causes some limitation of usual activities; the subject may experience annoying discomfort
- Severe: causes inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

AE causality (relationship guide)

Any AE has to be judged for causality (relationship to study medication and relationship to study procedure).

The relationship of an AE to the study product is to be graded on the basis of the following:

- Definite: a reaction that follows that follows a reasonable temporal sequence from study medication administration, abates upon discontinuation of the study medication (dechallenge), and is confirmed by reappearance of the reaction on repeat exposure
- Probable: a reaction that follows a reasonable temporal sequence from administration of the product; that follows a known response pattern to the suspected product; that is confirmed by an improvement on stopping the product; and that cannot be reasonably explained by the subject's clinical state
- Possible: a reaction that follows a reasonable temporal sequence from administration of the product; that follows a known response pattern to the suspected drug; but that may have been produced by the subject's clinical state or other therapeutic interventions on him/her
- Unlikely: a reaction that occurs with an improbable temporal sequence from administration of the product; that can be explained by the clinical state of the subject/participant or by other therapeutic interventions or other drugs or underlying disease providing plausible explanations.
- Unrelated: a reaction that occurs without a reasonable temporal sequence from administration of the product; that can be explained by the clinical state of the subject or by other therapeutic interventions on him/her and that does not improve or disappear following interruption of the product.

Handling of AEs

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the study product has to be discontinued if appropriate. Follow-up evaluations of the subject

are to be performed until the subject recovers or until the clinical investigator considers the situation to be no longer clinically significant.

If clinically significant laboratory abnormalities appear at the final visit, appropriate additional tests may to be performed to clarify the nature of any clinically significant laboratory abnormalities that occur.

AEs are monitored and registered on the AE form of the eCRF at each visit. In absence of a specific diagnosis, an individual AE form has to be filled in for each sign or symptom.

Persistent AEs will be entered once in the eCRF until they are resolved or if a new event has to be documented due to deterioration. These AEs will be carefully monitored; further details of monitoring of persistent AEs will be provided in the monitoring plan. If an AE is still not resolved at the end of the study, this will documented as ongoing.

For recurrent AEs, i.e., AEs of the same nature, but with a different date of onset, an individual AE form has to be completed for each of them.

AEs occurring up to 30 days after the last dose of study drug (and when reported by the subject) will be collected by study sites and reported to Sponsor even after the clinical trial has been finished if, in the judgment of the investigator, there is an association between the event and the previous use of the product under investigation.

If the AE is classified as serious, the clinical investigator has also to complete the SAE report form. It is the responsibility of the investigator or designee to send the SAE report form by fax or email to the CRO or designee within 24 hours and to retain the original copy of the form (keeping a photocopy in the Investigator Site File). At the earliest possible date, the SAE report form has to be followed by a detailed report and any documentation that may be available, e.g., hospital case records, autopsy reports, and/or other pertinent documents.

All the above documents will be sent by fax or email to the CRO within 24 hours of occurrence. The investigator will be responsible for reporting the SAE to ethics committees; the sponsor will be responsible for reporting the SAE to the respective health authorities, according to the national regulatory requirements.

Sponsor Medical Monitor for the study is:

[redacted]

The Safety Management Plan for specific countries will be written separately by respective CROs and the same will be followed.

Reporting Serious Adverse Events

Investigator Reporting of SAEs

Adverse events which are evaluated by the Investigator as "Serious" will be reported to the CRO within 24 hours of notice whether or not they are considered expected or drug-related. All SAEs will be reported as per local regulations. All Adverse Events encountered during the study will be reported on the appropriate form and summarized in the final report.

Any serious or unexpected adverse events should be reported to Respective CRO within 24 hours. For detailed safety information, refer to the safety plan or study manual. The CRO will report any Serious Adverse Event to the following or as per the safety plan.

Drug Safety Department

[redacted]

With copy to

Actavis Study Director

[redacted]

Watson Laboratories, Inc., USA
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054

[redacted]

Under 21 CFR 320.31(d)(3), the Sponsor or CRO must inform other investigators involved in the study plus the FDA within 15 days of becoming aware of the occurrence of the SAE. The CRO should report to the Medical Monitor and Sponsor within next 24 hours.

7.6 Laboratory Safety Measurements and Variables

The following laboratory variables will be analyzed at screening/Visit 1 and TOC/Visit 3:

Clinical chemistry (serum)	**Hematology (whole blood)**
Creatinine	Hemoglobin
Glucose	Platelet count
Total Protein	Total white blood cell (WBC) count
Sodium	Differential blood counts
Potassium	
Albumin	
Total bilirubin	
Alkaline phosphatase	
Aspartate aminotransferase	
Alanine aminotransferase	

A urinalysis will be performed per local practices; a urine pregnancy test (minimum sensitivity of 25IU/L) will be performed for female subjects of child-bearing potential at screening and at end of the study. A urine test for drugs of abuse will also be performed at screening.

Stool samples will be collected and analyzed for culture (at a minimum, *E coli*) and O&P (Ova and Parasites) at screening/Visit 1 and TOC/Visit 3 as described in the Study Manual or Lab Manual.

Laboratory analyses will be performed at local laboratories or central laboratories based on site's location**.**

7.7 Vital signs and Physical Examination

The investigator or designee will perform a brief physical examination at Visit 1 and Visit 3. The examination will include evaluation of the heart, lungs, abdomen, and eyes, ears, nose, and throat. Height, weight, and vital signs will be recorded on the eCRF. Vital signs are to include sitting blood pressure, pulse, and body temperature.

7.8 Procedures in Case of Medical Emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study.

7.9 Procedures in Case of Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies must be followed up and documented even if the subject was discontinued from the study.

Spontaneous miscarriages should also be reported and handled as SAEs.

If pregnancy is confirmed, the investigator must immediately terminate the study subject from the study but follow the study subject to determine the outcome and follow up the neonate for 8 week post delivery to know the outcome and health status of the neonate.

Protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy. Appropriate pregnancy follow-up procedures should be considered if indicated.

Reporting procedure

Pregnancy reporting process will be followed for pregnancies as per the local regulatory requirements. The guidelines for pregnancy reporting will be provided in a separate document (safety plan/ or study manual) to the clinical trial sites.

7.10 Appropriateness of Measurements

All clinical and laboratory procedures that will be used in this study are standard and generally accepted. All efficacy measurements are standard for studies of this indication.

8. Data Quality Assurance

Detailed procedures will be separately provided in the data management, monitoring, and quality plans.

Data Collection

All clinical study data has to be recorded in the eCRFs.

All subject data has to be reported on the eCRFs in an anonymous fashion. Subjects are identified only by subject number.

The investigator will be responsible for the completeness, accuracy, and legibility of the information in the eCRF and other study documents. For documents other than eCRF, only ballpoint pen is to be used and any change of data is to be done by striking out the incorrect data with a single line and dating and initialing the changes made.

The study monitors then have to check the eCRFs against the source documents for accuracy and validity as per the monitoring schedule, as applicable, including identification of any step in creation of source data such as when a computerized system is to be used to create, modify, maintain, archive, retrieve, or transmit source data.

The subject diary will remain as source at site and will only be source data verified by the monitors, but not collected. Source data verification will include the subject visit notes, diary data, eCRF data, and drug accountability. CROs will assign unblinded CRAs to perform the drug accountability.

Upon completion of the examination, eCRF completion is expected at each site to ensure quality of data and subject safety. Once eCRFs are completed, they will be available for review by the monitor and the designated CRO Clinical Data Management department. Completed eCRFs will be reviewed remotely for logical discrepancies. The monitor will ensure that all data queries and subsequent amendments in the eCRF documentation are made according to GCP guidelines.

A copy of the eCRF is to be archived by the investigator together with the study documents, source data, and laboratory records for the time required by the national regulation.

Site Audits

The Sponsor (or designee) may carry out an audit at any time. Investigators will be given adequate notice before the audit occurs. The purpose of an audit is to confirm that the study is conducted as per protocol, GCP, and applicable regulatory requirements, that the rights and well-being of the subjects enrolled have been protected, and that the data

relevant for the evaluation of the study drug have been captured, processed and reported in compliance with the planned arrangements. The investigator will permit direct access to all study documents, drug accountability records, medical records, and source data.

Regulatory authorities may perform an inspection of the study, even up to several years after its completion. If an inspection is announced, the Sponsor must be informed immediately.

Database Management

Lotus Labs will be responsible for the activities associated with the data management of this study, including the production of an eCRF, setting up a relevant database, along with appropriate validation of data and resolution of queries. All data will be entered into an eCRF. Automated and manual checks will be made against the data to ensure completeness and consistency. Resolution of queries will be implemented in the database.

AEs will be standardized for terminology and classification, using Medical Dictionary for Regulatory Activities (MedDRA, using the latest available version). Concomitant medications will be classified by site of action and therapeutic and clinical characteristics using the World Health Organization (WHO) Drug Dictionary (WHO-DD, using the latest available version).

9. Statistical Methods

9.1 Statistical and Analytical Plans

All items of the eCRF will be presented in individual subject data listings and in appropriate summary tables. Standard descriptive summary statistics will be calculated for continuous variables (i.e., arithmetic mean, standard deviation, minimum value, median, maximum value). Categorical data will be presented in frequency tables using counts and percentages. Individual subject data listings will be presented per parameter and will be sorted appropriately. Summary tables will be displayed by treatment group and visit (if applicable). Wherever appropriate, the presentation will include changes from baseline and shift tables.

Further details of the planned analyses will be given in the statistical analysis plan (SAP), which will be developed separately using this protocol. The SAP will give detailed descriptions of the statistical methods, models, hypotheses, and analysis populations to be analysed along with mock-shells for tables, listings and figures (TLF). The SAP will serve as a companion to the protocol and will serve as the de facto documentation of the proposed statistical evaluation.

9.2 Study Populations

The following 3 analysis populations will be defined for this study:

Safety Analysis Set: All randomized subjects who receive at least one dose of study drug will form the Safety Analysis Set. The Safety Analysis Set will be used for all analyses of safety, tolerability, and background characteristics.

Modified intent-to-treat (mITT) Set:

[redacted]

Per-Protocol (PP) Set: [redacted].

The PP analysis set is the primary analysis set for the assessment of bioequivalence between the test and the reference products.

[redacted].

Note: If a subject does not return for the scheduled TOC visit (24 to 72 hours after last dose of study medication [Day 5, 6 or 7]), then a telephone call should be made by the site and all efforts should be made to collect efficacy and safety data for Visit 3. This data should be entered in the eCRF for Visit 3.

9.3 Demography and Baseline Characteristics

All screening and baseline summaries will be provided for the safety analysis set and randomized population.

Ongoing and previous diseases in medical history will be summarized separately by system organ class (SOC) and preferred term. Coding will be based on MedDRA, using the latest available version.

Previous and concomitant medications will be coded according to WHO-DD (using the latest available version) and the verbatim term will be displayed together with the WHO-DD preferred term and the respective Anatomical Therapeutic Chemical (ATC) level 2 classification. Previous and concomitant medications will be summarized separately by ATC level 2 and preferred name.

Reasons for exclusion from each analysis set will be tabulated if warranted by results. Subject disposition status (randomized, treated, completed treatment, completed study) will be summarized by treatment group; reasons for discontinuation will be included in the disposition summary.

9.4 Analysis of Efficacy Parameters

9.4.1 Null Hypothesis for Primary Efficacy Parameter

Two sets of null hypotheses will be used for the primary efficacy endpoint to evaluate the clinical bioequivalence between test product and reference products with respect to the clinical cure rate using PP population. The hypothesis for testing equivalence is stated as below:

(i) Null Hypothesis for Bioequivalence:

$H_0 : p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

Versus

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

where p_T = clinical cure rate of test treatment and p_R = clinical cure rate of reference treatment.

The null hypothesis for bioequivalence will be evaluated based on the PP analysis set using two one-sided Z-test test with Yates correction, each at the 0.05 significance level. In practice, this is equivalent to constructing 90% confidence intervals (CIs) for the difference (test – reference) using a statistical model appropriate for the study design. If both intervals fall completely within the cutoff limits of [-0.20, +0.20] for clinical cure rates in this study, then equivalence is declared. Otherwise, equivalence is not declared.

The other null hypothesis will evaluate the differences between each active arm versus placebo as defined below:

(ii) Null Hypothesis for Superiority:

$H_0: p_T = p_P$

Versus

$H_1: p_T \neq p_P$

where p_T = clinical cure rate of subjects treated with rifaximin or Xifaxan® and p_P = clinical cure rate of subjects receiving placebo.

The objective of superiority test is to demonstrate that the test product and the reference product performed as expected (i.e. statistically superior to placebo) in the study. Hence, this null hypothesis serves as a validity to check the study sensitivity, after establishing the clinical bioequivalence between the test product and the reference product.

The null hypothesis for superiority analysis will be evaluated based on the mITT analysis set with LOCF for the missing data using a two-sided Z-test test with Yates correction with a significance level of α=0.05. Differences between the treatment groups and 95% CIs for the difference will be presented.

Note: Visit 2 data i.e. data from a telephone follow-up call on Day 3, after taking about 5 doses of study medication, may be considered for applying LOCF for mITT population, for the cases where TOC data is missing.

9.4.2 Null Hypothesis for Other Efficacy Parameters

Difference between groups in other efficacy endpoints will be examined as supportive/confirmatory analysis base on the following null hypothesis:

For categorical variables:

$H_0 : P_i = P_j$ vs $H_1: P_i \neq P_j$

Where P = proportion of subjects meeting the criteria, I and j = 1 (Test) , 2 (Reference), or 3 (Placebo) and $i \neq j$

For continuous variables:

$H_0 : \mu_i = \mu_j$ vs $H_1: \mu_i \neq \mu_j$

Where μ = group mean, i and j = 1 (Test), 2 (Reference), or 3 (Placebo) and $i \neq j$

All tests will be two-sided and performed at the 0.05 significance level. No adjustments will be made for multiplicity testing since all secondary efficacy endpoints are supportive/confirmatory.

9.4.3 Primary Efficacy Variable Analysis

The primary efficacy variable is the proportion of subjects who achieve clinical cure at the TOC visit (i.e., Study Day 5, 6 or 7).

To evaluate the null hypothesis (1) i.e., test for equivalence, the proportion of subjects meeting the clinical cure criteria will be tabulated by treatment group on the PP analysis set with LOCF*for missing data imputation. The differences between the test product and reference product on the PP analysis set will be estimated and the 90% CIs for the difference will be presented. The 90% CIs will be calculated using Z-test for proportion with Yates' correction as presented below.

$$L = (P_T - P_R) - 1.645\ se - (1/N_T - 1/N_R)/2$$

$$U = (P_T - P_R) + 1.645\ se + (1/N_T - 1/N_R)/2$$

$$P_T = C_T / N_T$$

$$P_R = C_R / N_R$$

$$se = SQRT\ [P_T*(1-P_T) / N_T + P_R*(1-P_R)/N_R]$$

Where C_T and C_R are number of subjects meeting the clinical cure criteria in the test product and the reference product arm respectively; P_T, P_R are the proportions of clinical cure from the test product arm and the reference product arm, respectively; N_T and N_R are total number of subjects in the analysis set from the test product and the reference arm product, respectively; se = standard error; SQRT = square root.

If the upper and the lower CIs are within the range of [-0.20, +0.20], the null hypotheses for clinical bioequivalence will be rejected and it can be claimed that the test product and the reference product are clinically equivalent with respect to the clinical cure rates.

Reasons for clinical failure will also be tabulated by treatment group showing the number and percentage of subjects failed by each criterion.

To evaluate the null hypothesis (2) i.e., test of superiority, the proportion of subjects meeting the clinical cure criteria will be tabulated based on the mITT analysis set with LOCF for missing data imputation. The differences between each active arm (test and reference) and the placebo group will be tested separately using a two-sided Z-test for proportion using Yates correction; the estimated difference and 95% CIs will be presented.

9.4.4 Secondary Efficacy Variables Analysis

All secondary efficacy endpoints will be tabulated by treatment groups on the mITT and PP populations.

For the secondary endpoint TLUS, defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed, summary tables will be presented along with p-values using appropriate statistical method.

For microbiological cure rate, summary tables will include number and percentage of subjects in each category; differences between groups (test vs placebo, reference vs placebo, and test vs reference) will be derived along with the 95% CIs for the difference using the Z-test for proportion to test the difference between the treatment groups; the Yates's correction will be applied for the calculation of 95% CIs.

For variables related to number of formed and number of unformed stools by study day, summary tables will include number and percentage of subjects with 0, 1, 2 … etc. number of stools by treatment group and time point. Stools occurred on Day 1 prior to receiving first dose of study drug will be included in the bowel movement at baseline; number of stools on Day 1 will include only those occurred on Day 1 after the first dose of study drug.

9.5 Analysis of Safety Parameters

All adverse events (AEs) and treatment-emergent AEs (TEAEs) reported during the study will be summarized/reviewed in order to assess safety. Safety will be evaluated by incidence of TEAEs including incidence of selected TEAEs of special interest, incidence of SAEs; TEAEs by relationship to study drug and intensity; and TEAEs leading to discontinuation. Observed results and change from baseline in clinical laboratory tests, vital signs, and physical examinations will be tabulated by treatment group.

MedDRA (using the latest available version) will be used to classify all AEs with respect to SOC and preferred term. All safety summaries will be performed on the safety analysis set by treatment group without inferential statistics.

Total extent of exposure to study drug will be measured by total number of tablets taken and duration of exposure calculated as date of last dose minus date of first dose plus 1. Study drug compliance (%) will be calculated as number of tablets taken divided by number of tablets expected to take multiplied by 100. Subjects are considered to have good compliance if the compliance (%) is within the range of ~75% to ~125%, corresponding to 7 to 11 doses.

9.6 Sample Size Calculation

The sample size calculation for this study is based on the published literature (CDER statistical review of NDA submission 21-361) and FDA's current guidance (FDA Guidance, 2004) on the clinical endpoint bioequivalence study of Rifaximin 200 mg. [redacted]

Thus, approximately 618 patient(s) [redacted] will be enrolled and randomized [redacted] for Test vs. Reference vs. Placebo [redacted]

[redacted] the overall dropout rate from the randomized patient population to mITT population does not exceed 15%. [redacted] he PP population when the lower and upper 90% CI falls within [-0.20, +0.20].

9.7 Handling of Drop-outs and Discontinuations

[redacted]

Missing data for other assessment (eg, safety assessment or baseline assessment) will not be imputed. However, for the purpose of summary, AEs with missing relationship to study drug assessment will be counted as "related"; AEs with missing intensity assessment will be counted as "severe". Missing intensity and relationship will be presented as is on the individual subject data listing.

9.8 Interim Analyses

No interim analysis is planned for this study.

9.9 Data Monitoring Board

A formal data monitoring board for safety and efficacy during the study will not be required.

10. Study Administration

10.1 Investigators and Study Administrative Structure

The Investigator who is responsible for the conduct of this study, in compliance with this protocol, is identified on the Investigator Agreement page. The Investigator will also provide a completed United States Food and Drug Administration (US FDA) Form 1572 to the Sponsor or Sponsor's representative prior to receipt of study drug and study initiation at that site.

Sponsor:	Actavis
Study Director	[redacted]
Contract Research Organization (CRO):	[redacted]
Project Lead (Lotus Labs)	[redacted]
Medical Monitor	[redacted]
Lead Biostatistician (Lotus Labs)	[redacted]
Contract Research Organization (CRO):	[redacted]
Project Manager (TCTM):	[redacted]
Contract Research Organization (CRO):	[redacted]
Project Manager (Chiltern):	[redacted]

10.2 Local Ethics Committee (LEC)/Institutional Review Board (IRB) Approval

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent form, and all other forms of subject information related to the study and any other necessary documents be reviewed by an LEC/ IRB.

It is required that a valid LEC/IRB approves in writing the conduct of this clinical study, together with the Investigator's informed consent document, prior to study initiation.
The trial protocol was developed in accordance with the Declaration of Helsinki, the ICH Guidance on GCP.

In performing this study, both the Investigator and Sponsor endorse, as a minimum, the standards for conduct of clinical research activities as set forth in the Declaration of Helsinki, ICH guidelines and local country laws and regulations.

The Investigator will submit the protocol and informed consent for LEC/IRB acceptance. This will be appropriately documented. The LEC/IRB should be asked to give its acceptance in writing. The names and qualifications of the members of the review committee will be recorded and submitted to the Sponsor, together with the written acceptance for the conduct of the study. The members of the LEC/IRB accepting must be independent of the Sponsor and the Investigator. The written acceptance should consist of a completed LEC/IRB acceptance form or written documentation from the containing the same information.

Until written acceptance by the LEC/IRB has been received by the Sponsor, no subject may undergo any procedures solely for the purpose of determining eligibility for this study.
Protocol amendments must also be reviewed and accepted by the LEC/IRB and written acceptance from the committee or at least the chairperson (or a designated committee member) must be received by the Sponsor before implementation. This written approval will consist of a completed LEC/IRB acceptance form or written documentation from the LEC/IRB containing the same information.

10.3 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, all ICH and GCP regulations governing clinical study conduct; ethical principles that have their origin in the Declaration of Helsinki and all applicable local laws and regulations. The investigator must assure that the study is conducted in accordance with the provisions as stated in the US FDA regulations and complies with prevailing local laws and customs.

10.4 Subject Information and Consent

The investigator or designee will explain the nature of the study to the subject, and answer all questions regarding this study, prior to obtaining informed consent.

The Investigator or designee will obtain informed consent from each subject enrolled in the study, in accordance with the Declaration of Helsinki, the current version of the ICH guidelines and the laws and regulations of the country in which the investigation is being conducted. In addition, study subjects must sign a HIPAA authorization, where required.

The LEC/IRB must accept the informed consent document to be used by the Investigator. It is the responsibility of the Investigator to assure that the subject has signed the informed consent form before any activity or treatment is undertaken. This includes, but is not limited to, the

performance of diagnostic or therapeutic procedures and the administration of the first dose of study medication.

10.5 Subject Confidentiality

Adequate records have to be maintained for the study, including subject medical records, eCRFs, laboratory reports, worksheets, nursing notes, signed informed consent forms, product forms, SAE forms, and information regarding subject discontinuation and reasons for discontinuation. The confidentiality of each record with subject identification is to be guaranteed by the clinical investigator.

This study protocol and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The investigator agrees to use this information only in conducting this study and is not allowed to use it for other purposes without written consent from the Sponsor. Results obtained from this study are the property of the Sponsor.

10.6 Study Monitoring

For protocol monitoring and compliance, a site initiation visit will be held prior to subject enrolment. The protocol, eCRF, IWRS entries, study treatment supplies, and study procedures will be explained in detail.

The purpose of monitoring is to verify the rights and well-being of human subjects are protected; that study data are accurate, complete, and verifiable with source data; and that the study is conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

A monitor assigned by the designated CRO will conduct regular site visits for the purpose of study monitoring.

The investigator must agree to allow the study monitor and authorized representatives of the designated CRO or the Sponsor to inspect all eCRFs and corresponding source documents (e.g., original medical records, subject records and laboratory raw data); to allow access to the clinical supplies, dispensing, and storage areas; and to agree to assist with their activities, if requested. The investigator should provide adequate time and space for monitoring visits.

The monitor will query any missing or spurious data with the investigator, which should be resolved in a timely manner. A visit log will be maintained to record each visit, the reason for the visit, the monitor’s signature, and the investigator’s or designee’s confirmation signature.

10.7 Case Report Forms and Study Records

Subject source documents are the physician's records maintained at the study site. The information collected on the eCRF must match those charts. In some cases, a portion of the source for a given subject may be the eCRF.

The eCRF data will be collected electronically. Instructions for entering data via internet will be provided in the eCRF Completion Guidelines and training will be provided to the study site staff prior to initiation of the site.

Periodically, the Monitor or other authorized Sponsor personnel will visit the study site for the purpose of comparing the data on the eCRF with the source documents. The Investigator agrees to make source documents available for this purpose. The eCRF should be completed as soon as possible after the data are available.

A minimum of the following set of documents will be received by the CRO prior to the initiation of the study:

1. Fully executed protocol
2. Debarment Letter
3. Completed and signed FDA Form 1572
4. Current curricula vitae, signed and dated for the Investigator and each Sub-Investigator named in the FDA Form 1572 (current within 2 years)
5. Current medical licenses of the Investigator and Sub-Investigators named in FDA Form 1572
6. Documentation of "No Objection" to proceed from the local regulatory agency, where ever applicable.
7. Documentation of LEC/IRB approval of this study protocol, Investigator and informed consent forms
8. Current LEC/IRB membership list or roster and EC SOPs
9. Financial Disclosure Statement for the Investigator and each Sub-Investigator named in FDA Form 1572
10. Sites Clinical Laboratory Head's current (within 2 years) curricula vitae and normal reference ranges of laboratory parameters
11. Fully executed Clinical Trial Agreement

10.8 Data Monitoring Committee

Not applicable.

10.9 Protocol Violations/Deviations

When a variation from the protocol is deemed necessary for an individual subject, the Investigator or other physician in attendance must contact the Sponsor's Medical Monitor or sponsor representative through the CRO representatives.

Such contact must be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. The deviation from the protocol will be authorized only for that subject.

All deviations related to study inclusion and exclusion criteria and significant deviations to subject management and protocol procedures must be documented on the appropriate eCRF.

Major protocol deviations/violations will include, but are not limited to, the following:

- Did not meet any critical inclusion/exclusion criteria which may impact the assessment of treatment efficacy.
- Did not receive randomized treatment (i.e., the actual treatment is not randomized treatment).
- Use of prohibited concomitant medications (e.g., prescription or OTC anti-diarrheal drug product, NSAIDs [with the exception of acetaminophen and paracetamol] or opioid analgesics).
- Did not meet the drug compliance of taking ≥ 7 to ≤ 11 doses.
- Did not come for Visit 3 within the visit window period of 24 to 72 hours of last dose.

10.10 Access to Source Documentation

Refer to Section 10.7.

10.11 Data Generation and Analysis

The majority of data is expected to be entered into the database via eCRF and any corrections will also be entered electronically. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary corrections will be made to the database and documented via addenda or audit trail. A manual review of selected line listings will also be performed at the end of the study.

10.12 Retention of Data

The investigator agrees to retain copies of the eCRFs with other study documents (e.g., the protocol and any protocol amendments, the Summary of Product Characteristics, LEC approval, signed consent forms, and source documents for each subject in the study [e.g., all demographic and medical information, including laboratory data, electrocardiograms,

medication disposal and subject diaries) in a secure place as long as needed to comply with national and international regulations. These records have to be made available for inspection upon reasonable request by a representative of the Sponsor or regulatory authorities.
If the Investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain written permission from the Sponsor before disposing of any records.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

10.13 Termination of the Study

The Sponsor reserves the right to terminate this study prematurely, either in its entirety or at a specific site, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to the Sponsor a reasonable time in advance of the intended termination. Neither party requires advance notice if the study is stopped due to safety concerns. If the Sponsor chooses to terminate the study for safety reasons, it will immediately notify the Investigator and subsequently provide written instructions for study termination. Subjects who have not completed treatment in the trial at the time of termination will be advised and offered alternative treatment, as medically indicated.

10.14 Financial Disclosure

Consistent with Title 21 CFR Part 54, all investigators will complete a Financial Disclosure Form that permits Sponsor to demonstrate that an Investigator has no personal or professional financial incentive regarding study outcome or the future approval or disapproval of an investigational drug such that the Investigator's research might be biased by such incentive.

10.15 Publication and Disclosure Policy

Any formal presentation or publication of data from this trial will be considered by the appropriate Sponsor personnel. For multicenter studies it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol. Investigators agree not to present data gathered from one center or a small group of centers before the full publication. In this case, the Sponsor must receive and approve the copies of any intended communication in advance of publication (at least 30 working days for an abstract or oral presentation and 60 working days for a journal submission). In any case, the Sponsor will review the publications/communications/abstracts for accuracy (thus avoiding

potential discrepancies with submissions to health authorities), verify that proprietary, confidential information is not being inadvertently divulged, and provide any relevant supplementary information.

10.16 Clinical Study Report

The clinical study report will be prepared as per ICH E3 format.

11 References

CDER Statistical review of NDA submission 21-361.

Center for Disease Control. cdc.gov/ncidod/dbmd/diseaseinfo/travelersdiarrhea_g.htm. 10 February 2014.

Food and Drug Administration, Draft Guidance on Rifaximin, November 2011.

Food and Drug Administration, Guidance for Industry Handling and Retention of BA and BE Testing Samples, May 2004.

Layer P, Andresen V. Review article. Rifaximin, a minimally absorbed oral antibacterial, for the treatment of travellers' diarrhea. Aliment Pharmacol Ther 31, 1155–1164

Xifaxan® (Rifaximin) tablets - 200 mg [package insert]. Raleigh, NC. Salix Pharmaceuticals, Inc; 2015.

12 Appendix - Detailed Protocol Summary of Changes

Administrative changes: Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment.

Other changes: Section numbers and titles in the table below refer to the current version of the protocol. Language that has been added to the previous version of the protocol is indicated in red text (example text). Language that has been deleted is indicated in red text with strikethrough (~~example text~~).

Section Number and Title; Rational for Change	**Old Version**	**Amended Version**
Section 3. Investigational Plan *Rationale for change: language added regarding stool collection if subject could not pass a stool sample at Visit 3*	Stool samples will be collected pre-treatment (screening) and post-treatment (TOC) to be cultured for pathogenic organisms. Adverse events (AEs), concomitant medication details and safety laboratory samples will be collected at Visit 1 and Visit 3.	Stool samples will be collected pre-treatment (screening) and post-treatment (TOC) to be cultured for pathogenic organisms. If the stool sample collection is not possible at visit 3, a rectal swab will be collected. Adverse events (AEs), concomitant medication details and safety laboratory samples will be collected at Visit 1 and Visit 3.
Section 4.2. Exclusion Criteria *Rationale for change: clarified use of opioids for criterion #5d.*	5d. Use of opioids within 48 hours preceding randomization.	5d. Use of opioids (in any form) within 48 hours preceding randomization.

Section Number and Title; Rational for Change	**Old Version**	**Amended Version**
Section 4.2. Exclusion Criteria *Rationale for change: added three exclusion criteria to provide timeframe for visiting country, excluding subjects with lactose and gluten intolerance and adding alcohol restriction*	6. Has a history or presence of allergic response to rifaximin or related drugs. 7. Has a current or recent history (within 12 months of screening) of drug or alcohol abuse.	6. Has a history or presence of allergic response to rifaximin or related drugs. 7. People who have lived in or stayed in the country where they acquired travelers' diarrhea for more than 6 months. 8. Has a history of lactose or gluten intolerance. 9. Consumed more than 2 alcoholic drinks within 12 hours before screening. Alcohol consumption is not allowed during the study. 10. Has a current or recent history (within 12 months of screening) of drug or alcohol abuse.

Section Number and Title; Rational for Change	Old Version	Amended Version
Section 4.3 Restrictions *Rationale for change: Added that alcohol and probiotics consumption would not be allowed; deleted the word "treatments" since alcohol consumption is not a treatment*	The following treatments are not allowed in this study: • Any antimicrobial agents with an expected activity against enteric bacterial pathogens within 7 days preceding randomization and during the study. • More than two doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents preceding randomization and during the study. • Use of any drug such as aspirin or ibuprofen (Advil), which can cause GI bleeding within 8 hours preceding randomization and during the study. Note: Acetaminophen (Tylenol) or paracetamol is acceptable for use during the study. • Opioids within 48 hours preceding randomization and during the study.	The following ~~treatments~~ are not allowed in this study: • Any antimicrobial agents with an expected activity against enteric bacterial pathogens within 7 days preceding randomization and during the study. • More than two doses of a symptomatic antidiarrheal compound such as antimotility agents, absorbent agents, and antisecretory agents preceding randomization and during the study. • Use of any drug such as aspirin or ibuprofen (Advil), which can cause GI bleeding within 8 hours preceding randomization and during the study. Note: Acetaminophen (Tylenol) or paracetamol is acceptable for use during the study. • Opioids (in any form) within 48 hours preceding randomization and during the study. • Alcohol or probiotics consumption.

Section Number and Title; Rational for Change	**Old Version**	**Amended Version**
Section 6.1 Schedule of Events, Table 1 – Schedule of Events *Rationale for change: Added footnote regarding stool collection if subject could not pass a stool sample at Visit 3*	N/A	Stool sample for culture and O & P: f. In case stool sample collection not possible at visit 3, a rectal swab will be collected.
Section 6.2 Screening, Randomization and Treatment Visit; Visit 1/ Day 1 *Rationale for change: Clarification that stool sample should be collected prior to study drug dosing*	Eligible subjects will be randomized and the first dose of study drug should be preferably administered under unblinded study staff/independent dispenser supervision at the clinic. The unblinded study staff/independent will dispense a total of 12 tablets from the containers and instruct the subjects to only take 9 tablets, and that the extra 3 tablets are provided only in case subject loses tablets.	Eligible subjects will be randomized and the first dose of study drug should be preferably administered under unblinded study staff/independent dispenser supervision at the clinic. Subjects should be suggested to start the first dose of the study drug only after providing the stool sample. The unblinded study staff/ independent dispenser will dispense a total of 12 tablets from the containers and instruct the subjects to only take 9 tablets, and that the extra 3 tablets are provided only in case subject loses tablets.

Section Number and Title; Rational for Change	**Old Version**	**Amended Version**
Section 6.5 Test of Cure; Visit 3 (Day 5, 6 or 7) *Rationale for change: added language regarding stool collection if subject could not pass a stool sample at Visit 3*	Subjects are to complete the study diary from day 1 until last study visit day.	Subjects are to complete the study diary from day 1 until last study visit day. If the stool sample collection is not possible at Visit 3, a rectal swab will be collected.