Statistical Analysis Plan with Amendment 02

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

**Statistical Analysis Plan with Amendment 02 Approval Date: 19 April 2017**

STATISTICAL ANALYSIS PLAN

PROTOCOL: ACTA/RIFX/2015 (Version 2, Amendment 2)

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
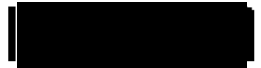
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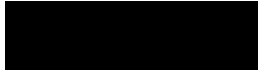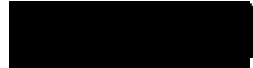
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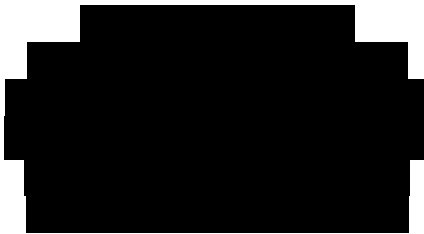
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Author(s):	████████████████████████
CRO for Biostatistics:	████████████████████
Sponsor:	**Watson Pharma Pvt. Ltd.** ████████████████████
Version:	03

REVISION HISTORY

Date of this version: 19-APR-2017

Version Number	Version Date	Previous Version Date	Summary of Changes
03	19 FEB 2017	09 FEB 2017	███████████████████████████████████ ██████ ███████████████████████████████████ █████████ ██ ███████████████████████████ █ ████████████████████████
02	09 FEB 2017	22 Aug 2016	**Section 3.1 Number of Study Sites:** This study will be conducted at approximately 30 study sites in approximately 3 countries. **Section 5.4 Per-Protocol (PP) Population:** ████████████████████████████████ ████████████████████████████████ ████████████████████████████████ ████████████████████████████████ ████████████████████ **Section 6 (d):** ████████████████████████████████ ████████████████████████████████ ████████████████████████████████ **Section 6 (e):** ████████████████████████████████

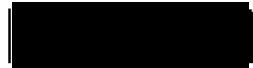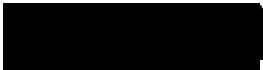|			████████████████████████████
			Section 7.5.1 Primary Efficacy Analysis: $L = (P_T - P_R) - 1.645 \, se - (1/N_T + 1/N_R)/2$ $U = (P_T - P_R) + 1.645 \, se + (1/N_T + 1/N_R)/2$ Section 8.8: Subjects Exclusion from the Efficacy Analysis: ████████████████████████ **Appendix I:** 14.2.2.5 Analysis of Microbiological Cure rates– Per protocol Population **Appendix II: Per-protocol population, point #3 Returned to the study site for Visit III after 24 hrs from time of last dose.** Consider the subjects who returned to visit III after 24 hours from the time of last dose; and had stool data up to 48 hours from the time of last dose. Subjects who did not enter any stool info in the diary after the last dose, but returned to visit III, will be considered as subjects did not have any stool sample for that particular period. Thus, subjects who did not report any stool sample within a period of 48 hours from the time of last dose with no fever, and with or without other enteric symptoms, will be considered in the clinical cure subjects list.
01	22 Aug 2016	N/A	N/A

APPROVALS

This document requires the following approvals:

Name	Title	Signature & Date
███████████	██████████ ████████.	
██████████	████████████ ████████	
█████████	████████ ████████	
█████████	██████████████ Actavis Inc	

*Signature by the Biostatistician responsible for development of the Plan and management of SAP activities for this study indicates: (1) study team validation of study requirements (2) approval, agreement, and commitment in support the plan for implementing these requirements. Signature by the Client/Sponsor appropriate personnel responsible for review and approval of the plan indicates: approval, agreement and commitment to support the plan.

TABLE OF CONTENTS

ABBREVIATIONS

Term	Abbreviation
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
eCRF	Electronic Case Report Form
CI	Confidence Interval
CRO	Contract Research Organization
DBL	Database Lock
FDA	Food and Drug Administration
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	modified intent-to-treat
PP	Per Protocol
P-Value	Probability value
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAEs	Treatment Emergent Adverse Events
TD	Travelers' Diarrhea
TLF	Table, Listing & Figure
TID	Three times a day
TLUS	Time to last unformed stool
TOC	Test of Cure
WHO-DD	World Health Organization Drug Dictionary

DEFINITIONS

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Concomitant Medication: A concomitant medication (con-med) is a drug, other than a study drug, taken by a subject after initial dose of study drug.

Database Lock: The point at which all clinical trial data has been reviewed, queries resolved, and issues addressed, and the database can no longer be changed in any manner; a locked database is ready to undergo statistical analysis.

Double-blind Study: A study in which neither the subject nor the investigator nor the research team knows what treatment a subject is receiving.

Dropout: A subject in a clinical trial who, for any reason, fails to continue in the trial until the last visit required of him/her by the study protocol.

eCRF: Audible electronic record designed to record information required by the clinical trial protocol to be reported to the sponsor on each trial subject.

Efficacy: The capacity of a drug or treatment to produce beneficial effects on the course or duration of a disease at the dose tested and against the illness for which it is designed.

Endpoint: An indicator or outcome measured in a subject or biological sample to assess the safety, efficacy, or other objective of a trial. Variable that pertains to the efficacy or safety evaluations of a trial.

p value: The lowest level of significance at which a given null hypothesis can be rejected; that is, the probability of observing a result as extreme or more extreme than that observed if the null hypothesis is true.

Prior Medication: A prior medication is a drug taken prior to the initial dose of study drug.

Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Serious Adverse event (SAE): Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Statistical Analysis Plan: A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

Statistical Significance: State that applies when a hypothesis is rejected. Whether or not a given result is significant depends on the significance level adopted.

Treatment-Emergent Adverse Event (TEAE): An event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.

Withdrawal: The act of reducing the degree of participation by a subject in a clinical trial. Subjects may withdraw permission for Sponsor use of data derived from study participation, privacy waivers, informed consent, or withdraw from active treatment component of a clinical trial but continue to be observed. Full withdrawal from participation in a study is called discontinuation.

1. INTRODUCTION

The purpose of this document is to provide details about the statistical analyses methods specified in the study protocol of ACTA/RIFX/2015 (Version 2, Amendment 2), and dated 06/Apr/2016. Detailed description of study objectives, study design, analysis populations, definitions of safety and efficacy endpoints, and details on statistical methods are provided in this document. Mock shells of tabulations and listings of efficacy and safety data will also be covered with this document as appendix. Any exploratory or additional analysis, apart from the methods specified in this document and the protocol, will be discussed in the clinical study report.

The Biostatistician is responsible for updating the SAP throughout the life cycle of the study as and when required. However, the first version of the SAP should be signed off before the database (DB) lock and any further changes should be addressed by the change control procedure such that the revised version of the SAP describes the change(s) along with rationale for those change(s) which are essential and would not compromise the quality and integrity of data or results. As this is a living document, changes will be made as needed. The responsible representative at Actavis will be required to review and approve all versions of the SAP.

2. STUDY OBJECTIVES

2.1 Primary Objective

Following are the **primary objectives** of this study:

(i)   Bioequivalence of rifaximin 200-mg tablets (the test product) and Xifaxan® 200-mg tablets (the reference product) with respect to the clinical cure rate within a period of 24 to 48 hr. from the time of last dose 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 (i.e., within 72 hrs from the time of first dose) is a clinical failure.

(ii)   Superiority of test and reference products over placebo with respect to the clinical cure rate within a period of 24 to 48 hr. from the time of last dose, in the treatment of TD, using the mITT population with LOCF.

2.2 Secondary Objective

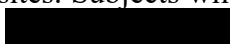Following are the **secondary objectives** of this study:

- To compare "Time to last unformed stool" (TLUS) observed for rifaximin 200-mg tablets and Xifaxan 200-mg tablets within a period of 120 hr. (last dose which is 72hrs, plus 48hrs). TLUS is defined as the interval beginning with the first dose of study drug and ending with the last unformed stool passed till 48 hour from the time of last dose.

- To compare the microbiological cure rate of rifaximin 200-mg tablets and Xifaxan 200-mg tablets on test of cure (TOC) visit. 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. STUDY OVERVIEW

3.1 Study Design

This is a randomized, double blind, placebo controlled, parallel design, multicenter bioequivalence study, designed to demonstrate

  i. Bioequivalence of Test (Rifaximin 200-mg Tablets) to Reference (Xifaxan® 200-mg Tablets) in the treatment of Travelers' Diarrhea.

  ii. Superiority of test and reference products over placebo with respect to the clinical cure rates within a period of 24 to 48 hr. from the time of last dose, in the treatment of TD, using the mITT population with LOCF.

Approximately six hundred eighteen (618) adult, non-indigenous travelers with naturally acquired acute diarrhea will be enrolled up to 40 sites. Subjects will be participating in the study for approximately 7 days and will be randomized ▮▮▮▮▮▮▮▮ 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 scheduled study visits will include:

Visit I: Screening, Randomization and Treatment Visit [Day 1 to Day 4]
Visit II: Telephone Visit [Day 3]
Visit III: Test of Cure Visit [>24 hrs from the time of last dose]

3.2 Investigational Medicinal Products

Test Product:
        Name of the product: Rifaximin
        Pharmaceutical dosage form: Film-coated oral tablets
        Strength: 200-mg

Manufactured by: Actavis Laboratories FL, Inc.

Reference Product:
Name of the product: Xifaxan
Pharmaceutical dosage form: Film-coated oral tablets
Strength: 200-mg
Manufactured by: Salix Pharmaceuticals, Inc. (Valeant Pharmaceuticals group of company)

Placebo:
Placebo tablets manufactured by Actavis Laboratories FL, Inc.

3.3 Study Drug Dosing

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.

3.4 Number of Study Sites

This study will be conducted at approximately 30 study sites in approximately 3 countries.

3.5 Number of Subjects

Approximately 618 ███████████████████████████████ will be randomized ███████ ██ ██████████████████████████████ assuming that the overall dropout rate from the randomized population to mITT population is about 15%.

3.6 Estimated Study Duration

Treatment duration for a subject is 3 days. A subject's participation in the study could be for duration of approximately 7 days.

3.7 Randomization and Blinding

All the study subjects will be randomly assigned ████████████████████████████ to receive either the test or the reference or Placebo. The original randomization schedule for this study is generated by CRO's third party vendor- ████████████, by a non-study-assigned independent expert using a computer generated automated process i.e. Interactive Web Response System (IWRS). All the IMPs will be handled by an independent dispenser at the site who will be unblinded with treatment arm, the subject is receiving. The study statistician and

programmers or other study personnel will have no access to the treatment codes until the final database is locked (DBL).

A dummy randomization will be used to program the TLFs before the DBL. Once the database is locked, original randomization schedule will be requested, after sponsor's approval, and utilized to create the final TLFs by meeting all the standard procedures. Unblinding the treatment code for any subject in middle of the study by investigator for safety reasons will not affect the creation of TLFs.

3.8   Schedule of Study Procedures

The schedule of study procedures is as presented in Table 1.

Table 1: Schedule of Study Procedures

Assessments	Screening, Randomization and Treatment	Treatment			TOC
	Day 1	Day 2	Day 3[a]	Day 4[b]	5, 6 or 7[c]
	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 after 24 hours from the time of 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

4. STUDY ENDPOINTS

4.1 Efficacy Endpoints

4.1.1 Primary Efficacy Endpoint

As per protocol, 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 (i.e., within 72 hrs from the time of first dose) is a clinical failure.

As per FDA's OGD guidance, the primary endpoint is clinical cure at the test of cure (TOC) visit on study Day 5, *with a window period of +/- one day*. In line with OGD, the protocol was designed such that the TOC visit should occur 24 to 72 hours after the last dose of study drug administration. After the study initiation, it was observed that some subjects were not able to complete the TOC visit within the above defined window period and a protocol deviation was filed to redefine the cut-off time point for evaluation of primary efficacy endpoint. Since, all the subjects were completing their diaries until the TOC visit and all the sites entered all diary data in the EDC that includes the data beyond the upper limit of window period for some subjects, decision was taken to consider 24 to 48 hour data for efficacy analysis. Thus, clinical cure rate was assessed on Visit-3 using subject's diary data from 24 to 48 hour period from the time of last dose when the drug is administered 3 times a day (TID) for 3 days in subjects with Travelers' Diarrhea (TD). Accordingly, clinical cure is re-defined as either of the following:

➢ No stools or only formed stools within a 48 hour period **from the last dose** with no fever, and with or without other enteric symptoms, OR

➢ No watery stools or no more than two soft stools passed within a 24 hour period **from the time of last dose** with no fever and no other enteric symptoms except for mild excess gas/flatulence.

This above decision was taken to standardize the data to be used for efficacy analysis and therefore there is no impact on the quality, safety & integrity of data due to the following reasons-

1. The evaluation of primary efficacy endpoint will be based on patient reported data and not the visit dependent clinician's evaluation.

2. This is a planned deviation for efficacy evaluation and will be applied to all the subjects.

4.1.2 Secondary Efficacy Endpoint

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 within a period of 120 hr. (last dose which is 72hrs, plus 48hrs).
    Mathematically, TLUS will be calculated as follows:
    TLUS (hours) = date/time of last unformed stool within 48hrs from the time of last dose – 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.

4.2 Safety Endpoints

The safety endpoints are:

1. Number and proportion of subjects reporting adverse events
2. Changes in clinical laboratory tests, vital signs, and physical examinations from baseline
3. Prior or Concomitant Medication
4. Medical History
5. Enteric symptoms

5. ANALYSIS POPULATION

4.3 Randomized population

Randomized population includes all the subjects who satisfies the inclusion and exclusion criteria and randomized into the study. This population may contain subjects who were randomized and have not consumed any drug. The assigned treatment group is used for the analysis.

4.4 Safety Population

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.

4.5 Modified intent-to-treat (mITT)

The modified intent-to-treat (mITT) is a subset of the safety analysis set consisting of all randomized subjects who meet all inclusion and none of the exclusion criteria, received at least one dose of study drug and provided efficacy and safety data after one dose of study drug. The mITT set is the basis for testing superiority of each active arm compared to the placebo with respect to primary efficacy endpoint i.e. clinical cure rate.

4.6 Per-Protocol (PP) Population
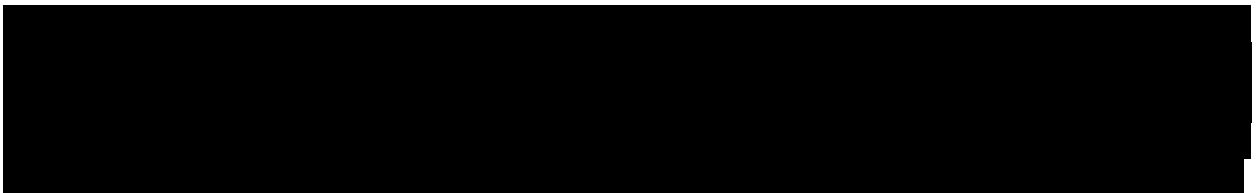
The PP analysis set is the primary analysis set for the assessment of bioequivalence between the test and the reference products.
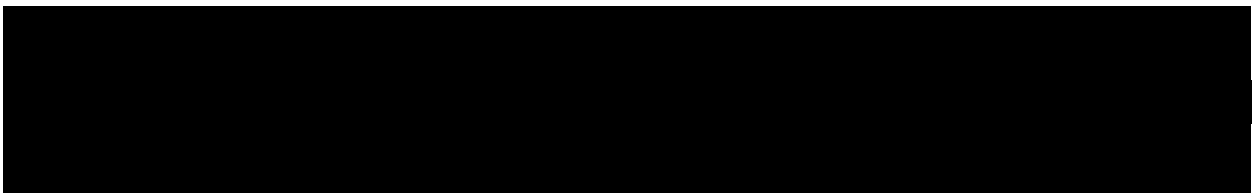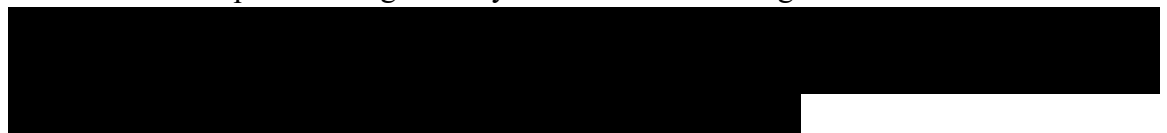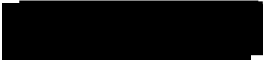
Subjects discontinued early for other reasons will be excluded from the PP population, but included in the mITT population, using LOCF.

6. HANDLING MISSING VALUES

LOCF will be used to impute missing efficacy data for the following situations.
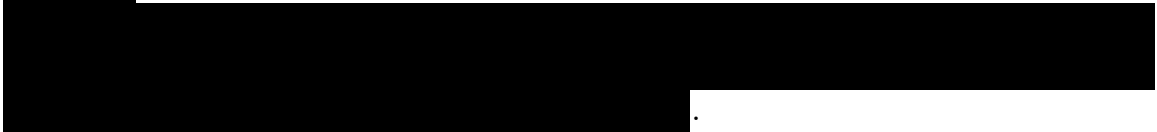
a.

b. ██
███
██████████████████

c. Subjects discontinued early for other reasons will be excluded from the PP population

d. ██
███
.

e. ██
███
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Missing data for other assessment (e.g., 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.

7. STATISTICAL METHODOLOGY

Unless otherwise explicitly stated, descriptive statistics for continuous variables are: n, mean, median, standard deviation, minimum and maximum. Descriptive statistics for categorical variables are: percentage, and the numerator (n) and the denominator (N) used in the percentage calculation.

7.1 Hypotheses and Decision Rules

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 Per-Protocol (PP) population. The hypothesis for testing equivalence is stated as below:

7.1.1 Primary Efficacy Analysis

(i) Hypothesis for Bioequivalence:

$$H_0 : p_T - p_R < -0.20 \text{ or } p_T - p_R > 0.20$$

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 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 cut-off limits of [-0.20, +0.20] for clinical cure rates in this study, then equivalence is declared. Otherwise, equivalence is not declared.

(ii)   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 $\alpha = 0.05$. Differences between the treatment groups and 95% CIs for the difference will be presented.

The tests for superiority will be conducted independently for test and reference products and superiority will be claimed if the two-sided p-value is found to be <0.05 at 5% level of significance for both, test and reference products separately; and the clinical cure rate is higher for the active drug(s) when compared with the placebo arm.

7.1.2   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:
$$H_0 : P_i = P_j \text{ vs } H_1: P_i \neq P_j$$
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:
$$H_0 : \mu_i = \mu_j \text{ vs } H_1: \mu_i \neq \mu_j$$
Where μ = group mean/median, 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.

## 7.2 Sample Size Justification

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. ████████████████████
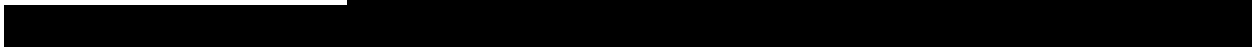
██ Superiority to be concluded when the lower bound of the two-sided 95% CI is greater than zero i.e. the 95% CI does not contain zero.
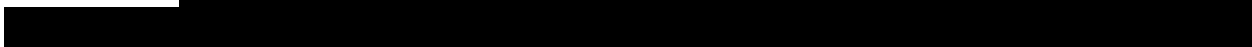
██ achieve at least 85% power to detect equivalence when the margin of equivalence for clinical cure rate extends from -0.20 to 0.20 (i.e. ± 20%).

██
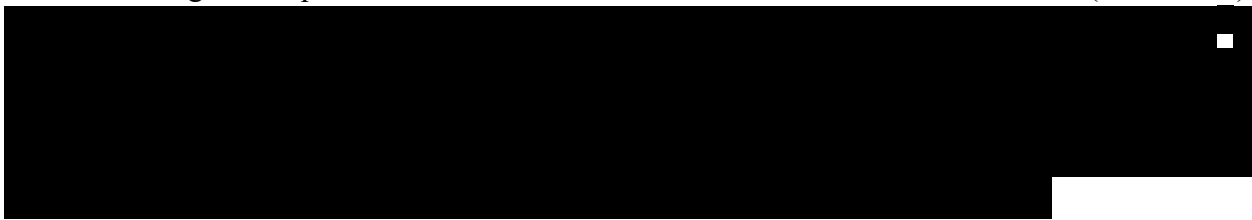
Thus, approximately 618 patient(s) ████████████████████████████ will be enrolled and randomized ██ the overall dropout rate from the randomized patient population to mITT population does not exceed 15%. ██ subjects in the PP population when the lower and upper 90% CI falls within [-0.20, +0.20].

1:1:1 Randomization

Thus, a total of 618 ████████████ subjects need to be enrolled and randomized ████████ ██ assuming that the dropout rate from the randomized to mITT population does not exceed 15%.
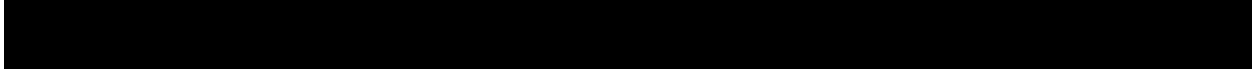
7.3 Exposure and Treatment Compliance

Subject compliance will be primarily monitored by counting the study tablets dispensed (Visit 1) and returned (Visit 3) compared to diary entries. 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.

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.

7.4 Interim Analysis

No interim analyses are planned in this study.

7.5 Efficacy Analysis

The following primary and secondary variables will be investigated in the evaluation of efficacy:

7.5.1 Primary Efficacy Analysis

The primary efficacy variable is the proportion of subjects who achieve clinical cure within 24 to 48 hours from the time of last dose.

To evaluate the null hypothesis (i) 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 (ii) 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.

7.5.2 Secondary Efficacy 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 within 48hrs from the time of last dose, summary tables will be presented.

A nonparametric test, Wilcoxon Rank-Sum Test, will be used for comparing the median TLUS difference between two treatment arms at 5% level of significance, without any adjustment for multiplicity. Additionally, Hodges-Lehmann estimate of location shift and Moses 95% confidence intervals will be calculated to assess the magnitude of median TLUS difference between two treatment arms at 5% level of significance.

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.

7.6 Safety Analysis

All Safety analysis will be summarized based on safety population and all safety summaries will be provided by treatment group.

7.6.1 Adverse Events

All AEs that occur during the study will be recorded. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1 or higher. Descriptions of

reactions or complaints will include the approximate time of onset, the time the AE ended, the severity of the AE, and the outcome. The Adverse Events (AEs) will be summarized by System Organ Class, preferred term, severity, and relationship to study drug.

All Adverse Event summary tables will list each event, the number of subjects in each treatment group in which the event occurred, and the rate of occurrences. The events will be grouped by System Organ Class and Preferred Term. Frequencies and percentages of patients experiencing TEAEs (Treatment Emergent Adverse Events) will be summarized by system organ class (SOC) and by preferred term within SOC for each treatment group. Additional summaries of AEs by severity and by relation to treatment will be tabulated by SOC and by MedDRA preferred term within SOC.

For AE summary tables, percentages would be based on the number of subjects in safety population in that particular treatment group. If a subject experienced more than one episode of an adverse event, the subject would be counted once for that event. If a patient had more than one adverse event in a system organ class, then the patient would be counted only once in that system organ class.

Serious Adverse Events (other than death but including the Serious Adverse Events temporally associated with or preceding the deaths) will be displayed in a summary table and listed. All Adverse Events or Serious Adverse Events which lead to withdraw from the study will be displayed in a summary table and listings.

7.6.2 Physical Examination

The number (%) of patients with screening physical examination abnormalities will be tabulated for the safety population and all physical examination data will be displayed in a listing by treatment group.

7.6.3 Vital Signs

Vital signs from each visit and the change from the baseline to each post-baseline visit will be summarized using descriptive statistics for the safety population. No formal inferential tests of significance will be performed. All vital signs data will be listed by treatment group and patient.

7.6.4 Laboratory investigations

Laboratory investigations of hematology, biochemistry and urine analysis tests performed for the safety population at screening (Visit I) will be repeated at TOC to ensure study subject safety and will be summarized accordingly.

7.6.5 Prior or Concomitant Medication

Incidence of prior or concomitant medications will be summarized by treatment group, and by the number and percentage of patients taking each medication, and will be classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

7.6.6 Medical History

Medical history will be captured at baseline and will be tabulated and listed by treatment group.

8. STUDY CONDUCT

This section details general conventions to be used for the statistical analyses. Departures from these general conventions may be given in the specific detailed sections of this analysis plan.

8.1 Subject Accountability and Disposition

The subject accountability and disposition information will be summarized for each treatment group. The subject accountability may include and not limited to number of subjects screened, enrolled, randomized, treated, discontinued before study completion and study completed. The subject disposition may include number of subjects in each population, study completion status and primary reason for discontinuation from the study. These summary reports will be generated using all randomized population and grouped by randomized treatment with total as a separate column.

8.2 Demographics and Baseline Characteristics

Demographic characteristics including age, gender, race, ethnicity, height, weight and body mass index (BMI) will be summarized by treatment groups for the safety, mITT & Per-Protocol population.

The comparability of treatment groups with regard to patient demographic characteristics will be evaluated using descriptive statistics. No inferential analyses are planned.

Gender, race, ethnicity will be summarized as frequency distribution by treatment group.

Patient's age in years at the time of consent will be derived as follows:
   Age = [(Date of Consent - Date of Birth) +1]/365.25 and truncated to completed years.

Baseline patient characteristics will include medical history and will be coded and tabulated by body system and preferred term using MedDRA, version 18.1 or higher.

Baseline and post-baseline patient characteristics will include physical examination, vital signs, and lab data, prior and concomitant medications.

Investigational product administration will be summarized for each patient and include total duration of exposure. Descriptive statistics including the mean, SD, minimum, and maximum will be provided by treatment group for safety population.

8.3 Study diary Completion

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; date/time of study drug
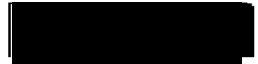
each dose; date, time and consistency of stool; as well as enteric infection symptoms (abdominal pain or cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, blood and/or mucus in the stool, tenesmus)

8.4 Enteric Infection and Other Symptoms

The number of subjects with enteric infection symptoms (abdominal pain or cramps, excessive gas/flatulence, nausea, vomiting, fecal urgency, blood and/or mucus in the stool, tenesmus) from the study diary and other symptoms (Fever, Moderate or severe dehydration) will be summarized and percentage will be calculated on mITT and per-protocol populations on all visits by treatment group.

8.5 Stool Data and Results

Number of formed and unformed bowel episodes will be listed per subject by treatment group and time on randomized population.

The number of subjects will be distributed to the corresponding frequency of formed and unformed bowel episodes by treatment group. The percentage will be calculated based on safety population.

Stool Culture Results of E.coli (ETEC & EAEC), Other Microorganism (example: Campylobacter, Salmonella, Shigella), Stool microscopy for ova and parasites will be summarized on the values of present or absent by treatment in Day 1 and TOC visits on mITT & Per-Protocol Population.

8.6 Protocol deviations

The following describes the protocol deviations that relate to statistical analyses or Per-protocol population.

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 or did not provide efficacy data for 24 hour to 48 hour period after the last dose.

A list of protocol deviations will be compiled prior to database closure for the primary analysis

and be updated prior to the analysis. The deviations will be listed on randomized population and also will be summarized on randomized population by treatment group.

Further, all the protocol deviations will be manually reviewed by the medical monitor of the study to determine whether any deviation is significant with respect to per-protocol population. Such deviations which may affect the treatment evaluation would be declared as "significant" protocol deviation by the medical monitor, and consequently these subjects will also be excluded from the per-protocol population for the primary efficacy analysis, in addition to above mentioned protocol deviations.

The medical monitor will send the significant protocol deviations to Biostatistics team in an excel sheet through email before DB lock. All these significant protocol deviations will also be submitted to regulatory in the form of XPT file along with the protocol deviations captured in the eCRF. The additional list of these protocol deviations will be prepared with respect to per-protocol population criteria and will be listed on randomized population by treatment group.

8.7 Analysis Conventions

The following conventions will be applied to all data presentations and analyses.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, standard deviation (SD), median, minimum and maximum values for continuous variables.

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented in the form xx (xx.x) where the percentage is in the parentheses.

- All summary tables will include the analysis population sample size (i.e., number of subjects).

- Change from baseline will be calculated as follows:
  Change = (baseline value)–(post-baseline value).

- All listings will be sorted for presentation by treatment and subject.

- Date variables will be formatted as DDMMMYYYY and time format is HH:MM for presentation.

- SAS Version 9.4 or higher will be the statistical software package used for all data analysis.

- A separate document with programming instructions will be prepared that will describe the derivation of these populations, before the database lock (DBL) or treatment unblinding for
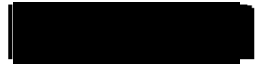
the study. This document will also include specifications and programming instructions for creating analysis datasets. An analysis dataset is a dataset created to answer specific analysis purposes which will include all the variables from raw dataset, population flags, treatment flags and some derived variables as per requirement.

8.8 Subjects Exclusion from the Efficacy Analysis

9 REFERENCES

1. Clinical Protocol of Rifaximin 200-mg Tablets [Protocol Number: ACTA/RIFX/2015, Protocol Version: Version 2 Amendment 2 dated 06/Apr/2016]

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

3. CDER Statistical review of NDA submission 21-361.

4. Statistical Principles For Clinical Trials (ICH E9)

APPENDIX I

Mock Shells: The TFL templates will be provided in a separate document.

APPENDIX II

PP Logic: Specifications and logic for the derivation of per-protocol population.

APPENDIX III

Analysis Data Specification: Detailed plan for derived variables (have specified attributes and definitions) to create TFLs on Subject-Level data and Basic Data Structure of domain wise analysis data will be prepared in a separated spread sheet document.