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

**Protocol Number:** 1526 RIF\_2 / NCT02920242

**Protocol Version, Date** Version 2.0, 29 Oct 2015



**Document Version, Date** FINAL 1.0, 26 May 2017

Prepared by:



On behalf of:

Sandoz GmbH

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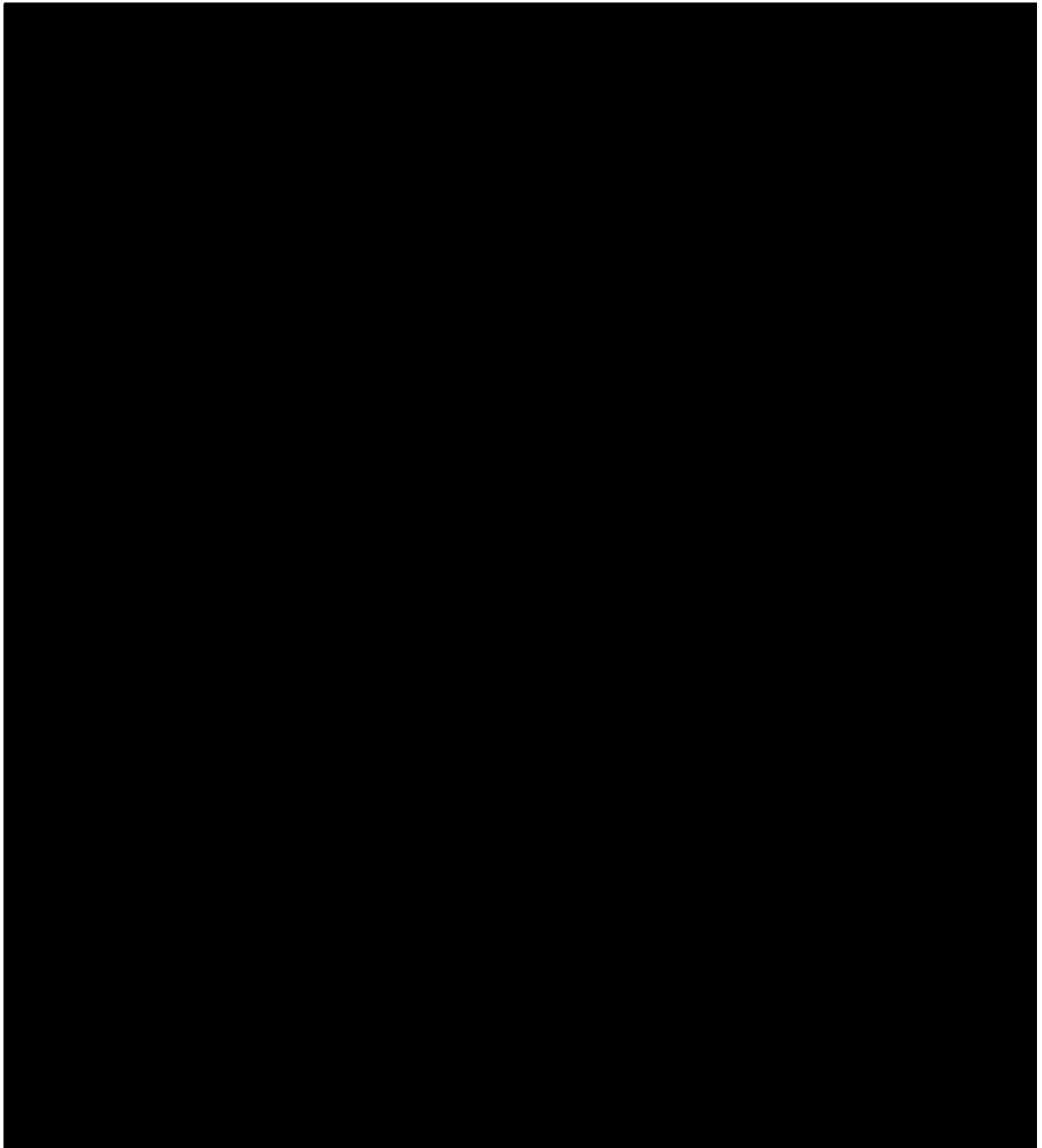


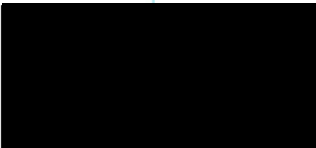
**Statistical Analysis Plan (SAP)**

**SANDOZ**

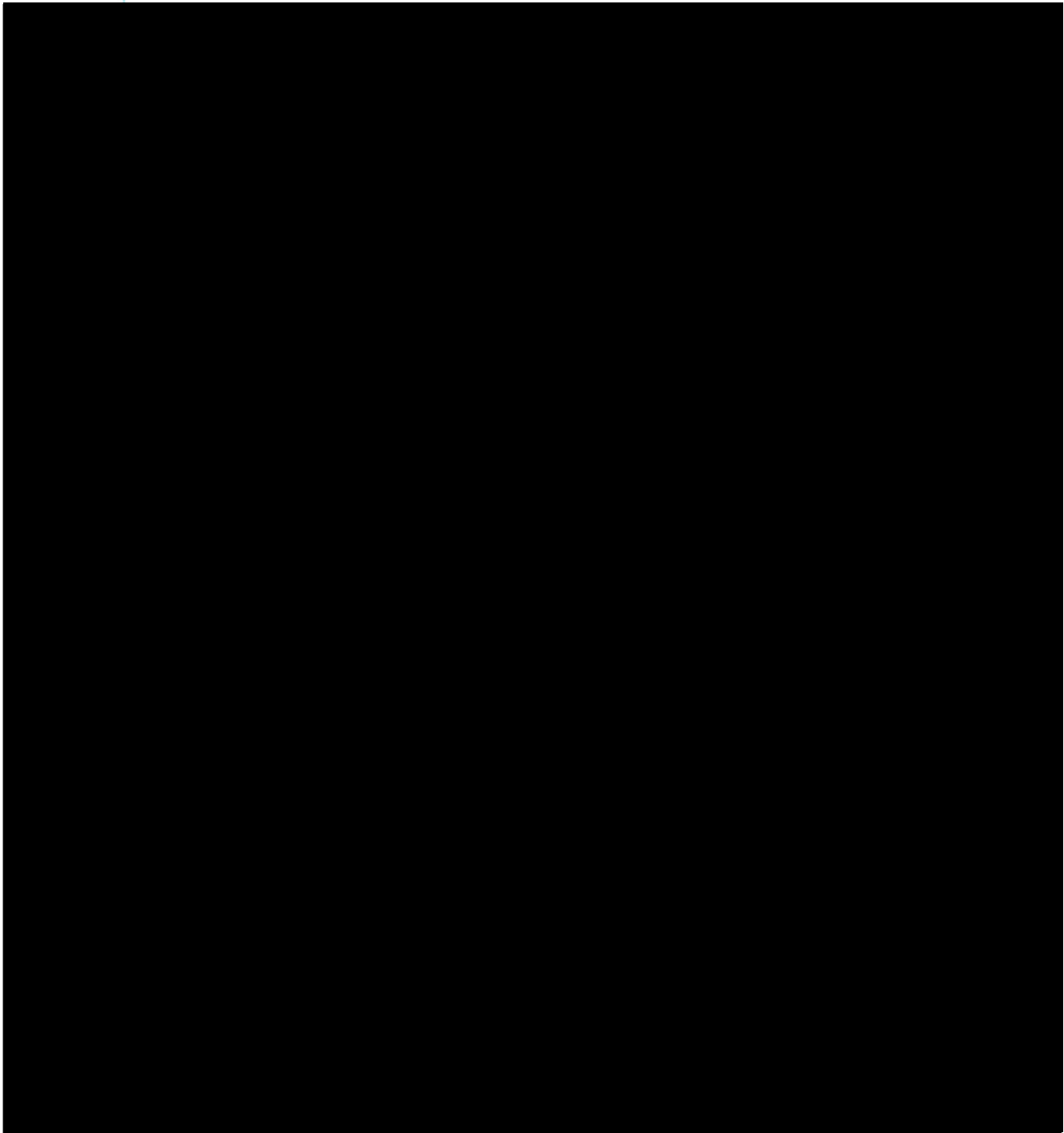
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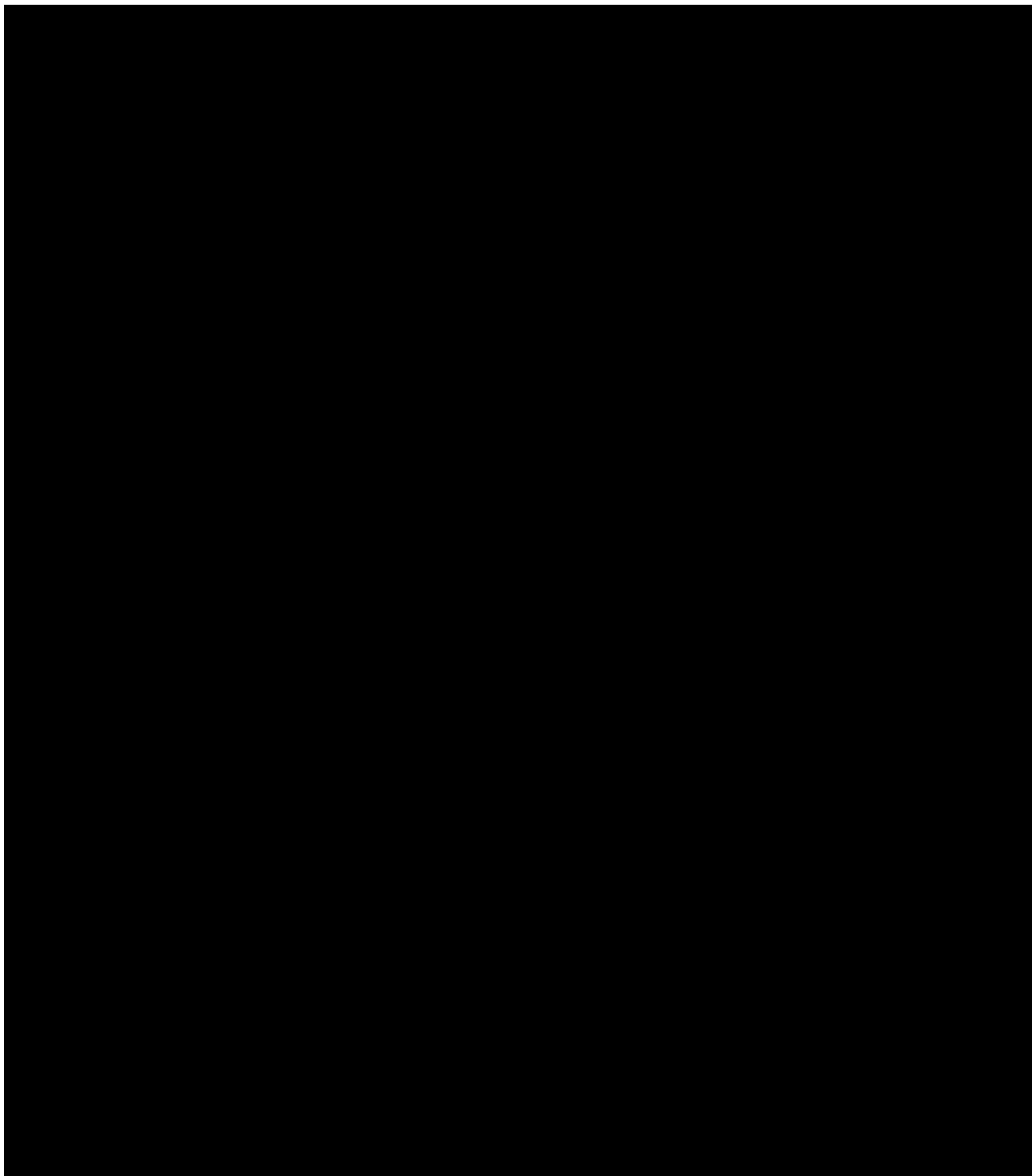


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## Statistical Analysis Plan (SAP)

**SANDOZ**

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### REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
1.0/26May2017	1.0	N/A	Original version

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**LIST OF ABBREVIATIONS**


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<b>Abbreviation or special term</b>	<b>Explanation</b>
AE	Adverse Event
ADR	Adverse Drug Reaction
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
eCRF	electronic Case Report Form
EOS	End of Study
GI	Gastrointestinal
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
PP	Per-Protocol
PT	Preferred Term
RLD	reference listed drug
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TD	Travelers' Diarrhea
TEAE	Treatment-Emergent Adverse Events





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TOC	Test of cure
USA	United States of America
WHO	World Health Organization

## 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the safety data derivations and data displays for study protocol 1526 RIF\_2, Version 2.0, titled "A randomized, double-blind, parallel group, placebo-controlled, multi-center, therapeutic equivalence study to compare Rifaximin 200 mg tablets (Sandoz GmbH) to Xifaxan® 200 mg tablets (Salix Pharmaceuticals, Inc.) and placebo in patients with travelers' diarrhea" dated 29 Oct 2015 for Final analysis. The SAP was prepared by [REDACTED] Biostatistics and Programming Department, specifically drafted by [REDACTED] [REDACTED] reviewed by [REDACTED] and [REDACTED]. Final analyses will be executed by [REDACTED].

[REDACTED]. The last patient last visit was on April 23<sup>rd</sup>, 2017. The final analysis, which will include only safety analysis due to low number of randomized patients, will be scheduled after the last patient has completed the 30 day safety follow up, and the resulting clinical database has been cleaned, quality-checked and locked.

The table of contents and templates for the TFLs will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) guidelines<sup>1,2</sup>.

All data analyses and generation of TFLs will be performed using SAS 9.3® or higher.

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## **2 STUDY OBJECTIVES**

### **2.1 Primary objectives**

The primary objective of this study is to demonstrate the therapeutic equivalence of Rifaximin 200 mg tablets to Xifaxan 200 mg tablets in patients with travelers' diarrhea (TD). In addition, the efficacy of Rifaximin and Xifaxan will be compared to Placebo to assess the assay sensitivity of the study.

### **2.2 Secondary objective**

The secondary objective of this study is to compare the safety and tolerability of Rifaximin 200 mg tablets to Xifaxan 200 mg tablets and to Placebo in patients with TD.

### **3 STUDY DESIGN**

#### **3.1 General study design**

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

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

Patients will undergo screening procedures at the study site and eligible patients will be randomized to one of the study treatments. Treatments administered (randomized in 2:2:1 ratio) are:

- Rifaximin 200 mg tablets
- Xifaxan 200 mg tablets
- Placebo tablets

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

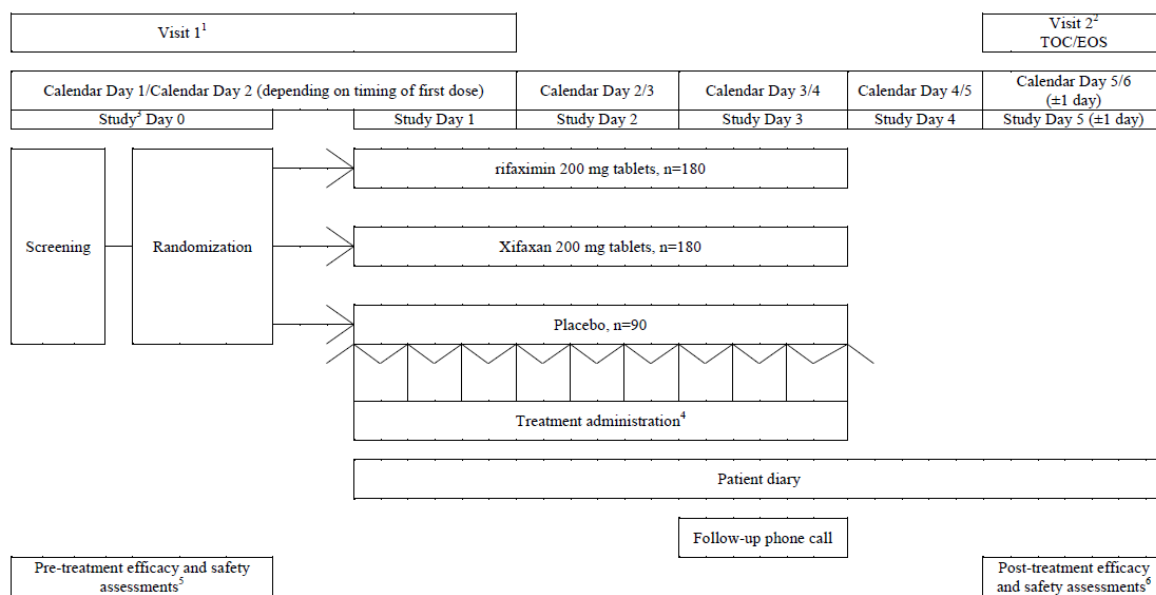
Patients will be contacted by telephone on Study Day 3 to determine if their condition has improved. Patients will return to the study site on Study Day 5 ( $\pm$  1 day) for the test of cure (TOC)/End of Study (EOS) visit. Patients will participate in the study for a maximum of 7 calendar days.

Patients will maintain an electronic Patient Diary daily for recording the date, time and form of all stools passed; the time and date of study drug administration; the presence or absence and severity of signs and symptoms of enteric infection; body temperature; and presence or absence of blood in the stool.

The use of any concomitant medications and the occurrence of any AEs will be recorded on a paper Supplemental Form.

A schematic presentation of study design is as shown in Figure 1.

**Figure 1: Study Flow Chart**



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

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

### **3.2 Randomization, blinding and unblinding**

At each study center, patients who are eligible to enter the double-blind treatment period will be randomized to generic Rifaximin 200 mg, Xifaxan 200 mg or matching Placebo according to a 2:2:1 randomization ratio through an Interactive Web Response System (IWRS).

The staff at the study center, the Sponsor and its representatives, and all patients will be blinded to the identity of the investigational product.

#### **3.2.1 Procedure for Breaking the Randomization Code**

The treatment code may be broken for an individual patient in the case of an emergency and when the knowledge of the investigational product is essential for the clinical management of the safety of this patient. The Investigator must make every effort to contact the Medical Monitor before breaking the treatment code. The Investigator will be able to access the IWRS database to receive the treatment code, 24 hours a day and 7 days a week. A record will be kept at each study center of all broken treatment codes, of the person who broke the treatment code, date, time and of the reasons for breaking the treatment code. In the case of a code break, the Investigator must inform the Sponsor or its representative immediately, without revealing to the Sponsor or its representative personnel the result of the code break.

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

### **3.3 Study treatments and assessments**

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

A detailed description of study procedures and assessments to be conducted during the study is provided in the protocol and summarized in the Schedule of Study Schedule/Flowchart in Table 1 below.

**Table 1: Schedule of Study Assessments**

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

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

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

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

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

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

4 To include hematology, clinical chemistry and urinalysis.

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

6 For female patients of childbearing potential (not post-menopausal or have not undergone surgical sterilization), the results of the urine pregnancy test must be negative to confirm eligibility prior to randomization.

7 The first dose of study drug is considered to be on Day 1, and is to be taken as soon as possible following completion of the Screening/Randomization procedures. The remaining 8 doses are to be taken at even intervals for 3 doses per day – a total of 9 doses of study drug are to be taken.

8 At Screening/Randomization, the patient will be given an electronic Patient Diary in which to record his/her symptoms; time of study drug administration; and date, time and form of all stools passed. The Patient Diary will be reviewed by the Investigator during the call on Study Day 3 at the TOC/EOS Visit.

9 Site will contact patient on Study Day 3 to check on their clinical status (i.e., if their condition has improved) and review completion of Diary and Supplemental Form. Information on AEs and concomitant medication will also be collected.

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10 Patients will be given a paper Supplemental Form for documentation of the administration of any concomitant medications or the occurrence of any AEs. The Form will be reviewed by the Investigator during the call on Study Day 3 and at the TOC/EOS Visit.

11 A follow-up phone call is to be performed should the patient have any ongoing AE at the TOC/EOS Visit. Any ongoing related AEs will be followed until resolution or until assessed by the Investigator to be permanent.



## 4 STUDY ENDPOINTS

### 4.1 Primary efficacy endpoints

The primary endpoint of this study is clinical cure at the TOC/EOS Visit (Study Day 5  $\pm$  1 day). Clinical cure is defined as either:

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

### 4.2 Secondary efficacy endpoints

Following are the secondary endpoints in this study:

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

### 4.3 Safety endpoints

The safety endpoints in this study are:

1. Incidence of reported adverse events (AEs)
2. Changes in vital signs and clinical laboratory parameters

## 5 SAMPLE SIZE AND POWER

According to the FDA Draft Guidance on rifaximin<sup>3</sup> sample sizes should be chosen such that the power is sufficient to establish therapeutic equivalence between generic and RLD rifaximin (Xifaxan) and sufficient to show that both are active compared to placebo (study sensitivity). Therapeutic equivalence is to be shown for the PP (per protocol) population whereas study sensitivity is to be shown for the modified Intent to Treat (mITT) population.

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

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

- [REDACTED]
- [REDACTED]

Concerning the assessment of study sensitivity, a sample size of 170 in the generic Rifaximin group and Xifaxan® group and 85 in the Placebo group achieve approximately [REDACTED] power to detect a difference between the group proportions of [REDACTED], assuming that:

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

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

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## **6 ANALYSIS POPULATIONS**

### **6.1 Safety Population**

The Safety population includes all randomized patients who received at least 1 dose of the study product. In this population, treatment will be assigned based upon the treatment patients actually receive regardless of the treatment to which they were randomized. The safety population will be used for safety analyses.

## 7 STATISTICAL CONSIDERATIONS AND ANALYSIS

### 7.1 Derived Variables

The below table provide the list of derived variables for duration derivations, drug compliance, baseline derivations and other important derivations applicable for this study.

Variables	Formula
<b>Derivation of Duration</b>	
Study day	Study days will be based on the day and time of first administration of study drug which is Day 1. Subsequent study days will be calculated as 24 hours interval from the first dose.
Duration of Study Drug (hours)	The date/time of last dose – date/time of first dose rounded to hours
<b>Drug Compliance</b>	
Compliance	$\frac{\text{(Number of tablets taken)}}{\text{(Number of scheduled tablets)}} \times 100$ <p>For a patient that drops out early, the number of scheduled tablets should be the number the patient should have taken till the time subject dropped out.</p>
<b>Baseline Derivations</b>	
Baseline	Baseline is defined as the last non-missing assessment prior to start of the first study drug administration.
Change from baseline	Post baseline value – Baseline
Percent change from baseline	$\frac{[(\text{Post baseline value} - \text{Baseline})/\text{Baseline}]}{1} \times 100$

### 7.2 Definitions

#### 7.2.1 Definitions relative to safety criteria/AEs

##### 7.2.1.1 Adverse Event (AE)

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

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use

of a medicinal product, whether or not considered related to the medicinal product.

#### **7.2.1.2 Serious Adverse Event (SAE)**

A SAE is any AE that:

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

Whether AE is serious and the seriousness criteria met will be collected on eCRF.

#### **7.2.1.3 Pre-treatment AEs, Treatment-emergent AEs**

- An AE is defined as pre-treatment if its onset date/time is before the date/time of the first intake of study medication
- An AE is defined as treatment-emergent if its onset date/time is on or after the date/time of the first intake of study medication or if a pre-existing condition becomes worse after the date/time of first intake of study drug.

#### **7.2.1.4 Treatment-related AEs**

Relationship of AE with study drug is recorded on eCRF page with options “Suspected”, “Not Suspected”, and “Not Applicable”. Any AE with “Suspected” relationship to the study drug will be considered as treatment-related.

### **7.3 Handling of missing data and outliers**

Missing safety data will not be imputed and will be presented as observed.

#### **7.3.1 Missing data analysis methods**

Not Applicable.

## **8 STATISTICAL METHODS**

### **8.1 General statistical conventions**

All data analyses will be performed using the SAS® software package version 9.3 or higher.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Categorical data will be described using count and frequency. Percentages will be rounded to one decimal place. Shift tables will be provided, where appropriate.

All analyses and summaries will be presented by treatment group, unless otherwise specified.

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

- Diagnoses: Medical Dictionary for Regulatory Activities (MedDRA) v18.1
- Medications: World Health Organization (WHO) Drug Dictionary including Anatomical Therapeutic Chemical (ATC) classification Sept 2014
- AEs: MedDRA v18.1

All patient data, including those derived, will be presented in individual patient data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only. All listings will be sorted by investigational site, patient number, date/time and visit. The actual treatment group as well as patient's sex and age will be stated on each listing. Unless otherwise stated, data listings will include all patients in Safety population.

## 8.2 Patient disposition

Patient disposition information will be summarized by treatment group and overall. The number of patients screened, the number and percent of patients who are screen failure, randomized, who took a dose of study drug, who were randomized and not treated, who complete the study and who withdraw early from the study will be presented. Screen failure percentage is calculated from number of screened patients and other percentages are calculated among number of randomized patients. Patients from Safety Population will be summarized using descriptive statistics displaying number and percentage. Percentage will be done using the number of randomized as denominator.

The primary reason for early withdrawal will also be summarized by treatment group in Safety Population.

Patient disposition will be listed for all patients screened.

Treatment Misallocations:

If a subject was:

- Randomized but not treated, they are by definition excluded from the safety analyses as not receive at least of one dose of study drug.
- Randomized but took incorrect treatment, then they will be reported under the treatment they actually received for all safety analyses.

## 8.3 Protocol deviations

A listing will include the inclusion/exclusion criteria violated at Screening/Randomization as well as other protocol deviations identified based on data recorded on the eCRF and/or protocol deviation Logs from [REDACTED] Medical for all randomized patients.

Major protocol deviations defined as below will be listed separately:

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

## 8.4 Demographics and baseline characteristics

### 8.4.1 Demographics

Age, height, weight, BMI, the number of formed stools in the past 24 hours at baseline, the number of unformed stools in the past 24 hours at baseline, and the duration (days) in the host country will be summarized descriptively. Sex, Race, Ethnicity, country of residence, signs and symptoms of enteric infection (abdominal pain or cramps, nausea, vomiting,

fecal urgency, gas/flatulence, and tenesmus), and pathogen status (inflammatory/invasive pathogens, diarrheagenic *E Coli* group without evidence of inflammatory/invasive pathogens, other pathogens without evidence of inflammatory/invasive pathogens) at baseline will be summarized. Safety population will be used for reporting.

#### 8.4.2 Medical history

Listing for medical history will be presented by system organ class (SOC) and preferred term (PT) Medical Dictionary for Regulatory Affairs® (MedDRA) Version 19.0 or higher.

#### 8.4.3 Prior and concomitant medications

Prior medications are defined as those medications with a start date prior to the first dose of study drug. Concomitant medications are defined as those medications with a start date on or after the first dose of study drug. Prior medications were recorded in medical history at the Screening/Randomization visit. The administration of any concomitant medication or herbal/dietary supplements during the study will be recorded by patients on the Supplemental Form provided at the Screening/Randomization Visit. The form will be reviewed by the Investigator during the call on Study Day 3 and at the TOC/EOS Visit. Prior and concomitant medications will be recorded on the eCRF by the investigator. Prior and concomitant medications used in this study will be coded by using the latest available version of the World Health Organization (WHO) Drug Dictionary including Anatomical Therapeutic Chemical (ATC) classification.

Listing for prior and concomitant medications will be presented.

### 8.5 Extent of exposure

#### 8.5.1 Treatment duration

At TOC/EOS Visit, the date/time of first dose and last dose, in addition to the actual total number of tablets taken will be recorded in the eCRF. Duration of study drug (in hours) will be the date/time of last dose – date/time of first dose rounded to hours.

Study drug exposure will be summarised by treatment group on the Safety Population using descriptive statistics.

The actual total number of tablets taken will be summarized by treatment group using descriptive statistics.

#### 8.5.2 Treatment compliance

Treatment compliance in this study will be monitored by tablet count as described in section 7.1.



Summary of treatment compliance will be presented by treatment group by the number of subjects (n), mean, standard deviation, median, min, and max. They will also be summarized in categories “< 75%”, “75-125%” and “> 125%” using frequency tables.

Treatment compliance will be summarized and listed based on the Safety Population.

## 8.6 Safety analyses

All definitions relative to safety endpoints are detailed in Section 7.2.1

Safety analyses will be conducted on the Safety Population (treated patients) and will be performed for all safety variables specified below.

All safety data will be summarized by treatment group and overall.

The safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters, vital signs, and physical examination) will only include patients from the Safety Population who have data available for both the baseline and the time point under consideration unless otherwise specified.

No statistical test will be performed.

### 8.6.1 Adverse events

All Adverse events (AEs) will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 or higher.

Incidences of Treatment-Emergent Adverse Events (TEAEs) will be tabulated by SOC and PT. Incidences of TEAEs will also be presented by maximum severity (intensity), seriousness and relatedness to study drug. Subjects who discontinued due to AEs will be summarized by SOC and PT in a separate table. Patients are counted only once in each SOC, and only once in each PT category. The table will be sorted in alphabetical order by SOC and in decreasing frequency of PT based on total reports within each SOC.

In summary, the following tables will be developed for summarizing AEs.

- Overall summary of TEAEs, it includes number and percentage of subjects with any TEAEs, subjects with any treatment-emergent SAE, subjects with any severe TEAEs, subjects with any treatment-related TEAEs, subjects with TEAEs leading to study discontinuation, subjects with death.
- Summary of TEAEs by SOC and PT
- Summary of treatment-emergent SAEs by SOC and PT
- Summary of TEAEs by SOC and PT and maximum severity
- Summary of TEAEs by SOC and PT (treatment-related)
- Summary of treatment-emergent SAEs by SOC and PT (treatment-related)

- Summary of TEAEs by SOC and PT and maximum severity (treatment-related)
- Discontinuations due to TEAEs by SOC and PT
- Death due to TEAEs by SOC and PT

In addition, an overall summary for the categories above will be prepared by treatment group and overall.

Individual patient data listings will be provided for those with non-treatment emergent AEs, TEAEs, treatment-emergent SAEs, treatment-related TEAEs, deaths, and discontinuation due to AEs.

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

### **8.6.2 Clinical laboratory evaluations**

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

Hematology, blood chemistry and urine samples will be collected at Screening/Randomization Visit and TOC/EOS Visit. Urine pregnancy test will be done on all females of child bearing potential (not post-menopausal or not surgically sterile) prior to randomization at Screening/Randomization Visit and at TOC/EOS Visit. If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used. For the purposes of summarization in both the tables and listings, all laboratory values will be presented in SI units. If a lab value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

Please refer to protocol section 12.4 for detailed list of parameters collected in blood samples for analyses. Summary statistics of measurements, change from baseline values, percent change from baseline values for hematology, chemistry, and urinary parameters will be presented at Screening/Randomization Visit and TOC/EOS Visit by treatment group. Shift tables displaying changes with respect to the normal range between baseline and TOC/EOS Visit will be provided. A listing of all subjects with abnormal values at any time point will be given.

### **8.6.3 Vital signs**

Vital signs (body temperature, blood pressure, heart rate, respiratory rate) will be measured at Screening/Randomization Visit, TOC/EOS Visit and unscheduled visit. Vital

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sign measurements at baseline and TOC/EOS Visit, and change at TOC/EOS Visit from baseline will be summarized by visit and treatment group.

A patient data listing of all clinically significant abnormal vital signs, including findings from unscheduled visits, will be provided.

#### **8.6.4 Physical examinations**

Physical examinations will be performed at Screening/Randomization Visit, TOC/EOS Visit and unscheduled visit. Shifts (normal, abnormal, not done) from baseline to TOC/EOS Visit will be summarized using patient counts and percentages.


A patient data listing of all physical examination abnormal findings, including findings from unscheduled visits, will be provided.

#### **8.7 Interim analysis**

Not applicable

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## **9        CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL**

 This SAP v1.0 excludes efficacy analyses from the final analyses due to low number of randomized patients.

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**10 REFERENCES**

- 1) ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95-adopted December 1995).
- 2) ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).
- 3) Draft Guidance on Rifaximin, recommended February 2012.

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## **11 APPENDICES**

### **Appendix A – Interim Analysis**

Not Applicable



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**Appendix B - Visit Window**

Not Applicable