Statistical Analysis Plan

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF RIFAXIMIN SOLUBLE SOLID DISPERSION (SSD) TABLETS FOR THE DELAY OF ENCEPHALOPATHY DECOMPENSATION IN CIRRHOSIS (REDC)

Protocol Number: RNLC3131

Author: Eric Nowicki

Sr. Director, Biostatistics

Statistics & Data Corporation

Date: 11JUL2025

Version: 1.0

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SAP Date: **11JUL2025**

Statistical Analysis Plan Approval

Prepared by:

Signed by:
Eric Nowicki
Signer Name: Eric Nowicki
Signing Reason: I approve this document
Signing Time: 11-Jul-2025 | 14:27 MST
5C19D6C71439498583E0A1FA39DB802E

11-Jul-2025 | 14:27 MST

Eric Nowicki, Ph.D. Date

Sr. Director, Biostatistics

Statistics & Data Corporation

Reviewed by:

Signed by:
Adam Hamm
Signer Name: Adam Hamm
Signing Reason: I approve this document
Signing Time: 11-Jul-2025 | 18:25 EDT
7172A98667634ABDA891733B785152E8

11-Jul-2025 | 18:25 EDT

Adam Hamm, Ph.D. Date

Sr. VP, Biostatistics and Strategic Consulting

Statistics & Data Corporation

Approved by:

Signed by:
James Yuan
Signer Name: James Yuan
Signing Reason: I approve this document
Signing Time: 11-Jul-2025 | 14:31 MST
13D58932CF914FA291FCC989B416AA39

11-Jul-2025 | 14:31 MST

James Yuan, Ph.D. Date

Director, Biostatistics

Bausch Health US, LLC

Document History

Date	Version Number	Summary of Changes or updates
11 Jul 2025	1.0	

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Abbreviations

Abbreviation	Description
AE	Adverse Event
AKI- HRS	Acute Kidney Injury-Hepatorenal Syndrome
CAT	Computer Adaptive Test
CEAC	Clinical Event Adjudication Committee
CLD	Chronic Liver Disease
CTCAE	Common Terminology Criteria For Adverse Events
DRESS	Drug Rash With Eosinophilia And Systemic Symptom
EC	Ethics Committee
EOS	End Of Study
EVB	Esophageal Variceal Bleeding
HCC	Hepatocellular Carcinoma
HE	Hepatic Encephalopathy
HRS	Hepatorenal Syndrome
ICF	Informed Consent Form
IRB	Institutional Review Board
ITT	Intent-To-Treat
MELD-Na	Model End Stage Liver Disease-Sodium
OHE	Overt Hepatic Encephalopathy
PK	Pharmacokinetic
PP	Per Protocol
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Preferred Term
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Spontaneous Bacterial Peritonitis
SD	Standard Deviation
SOC	System Organ Class
SSD	Soluble Solid Dispersion
TEAEs	Treatment-Emergent Adverse Events
TIPS	Transjugular Intrahepatic Portosystemic Shunt
WHO DD	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze, and report results for Protocol No. ***RNLC3131***. The Protocol Version 5.0 (Amendment 4.0) dated 14 Dec 2022 is used to develop this SAP.

2. Study Background and Overview

Rifaximin 550 mg (tablets) is approved by the FDA to reduce the risk of OHE recurrence in patients ≥ 18 years of age. It is not indicated for primary prophylaxis of OHE. The current literature supports the potential therapeutic utility of rifaximin in treating initial complications of cirrhosis such as SBP, HE, and esophageal variceal bleeding (EVB) through multiple mechanisms (Elfert, 2016; Menshawy, 2019), including direct suppression of intestinal bacterial overgrowth and bacterial translocation that leads to a reduction in endotoxemia, bacteremia, and bacterial seeding of ascitic fluid, and indirect improvement in portal hemodynamics (Komolafe, 2020; Lv, 2020; Ponziani, 2015). While the efficacy of broad-spectrum antibiotics for the treatment and prophylaxis of cirrhosis complications such as SBP is well documented, they have high systemic exposures and there is concern over the emergence of drug-resistant organisms (Glaess, 2019).

Data support the potential clinical utility of rifaximin in delaying decompensation to OHE in cirrhosis (Ponziani, 2015). Based on these data and given the need for safe and effective alternatives to systemic broad-spectrum antibiotics used to treat complications of cirrhosis, this Phase 3 trial is being conducted to assess the viability of rifaximin SSD-40IR to delay encephalopathy decompensation.

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objective of this study is to assess the efficacy of rifaximin SSD-40IR versus placebo to delay the occurrence of HE.

2.1.2 Secondary Objectives

The secondary objective of this study is to assess the effects of treatment with rifaximin SSD-40IR on hospitalization rates.

2.1.3 Safety Objectives

The safety objective of this study is to assess the safety of rifaximin SSD-40IR following a treatment regimen of 72 weeks.

2.1.4 Exploratory Objectives

The exploratory objectives of this study are:

- To determine the population PK of rifaximin following administration of rifaximin SSD-40IR and to compare the PK profiles of rifaximin and 25-desacetyl rifaximin on Visit 2/Day 1 and Visit 3/Week 4 by noncompartmental analysis of participants in the PK substudy. Approximately 10 participants per treatment group will participate in

serial PK sampling at selected sites. The remaining participants will have sparse PK samples collected.

- To monitor the resistance of predetermined bacterial species to rifaximin and rifampin over the study period to ascertain the long-term effects of rifaximin. Approximately 25 participants per treatment group will participate in the bacterial resistance substudy.

2.2 Study Design

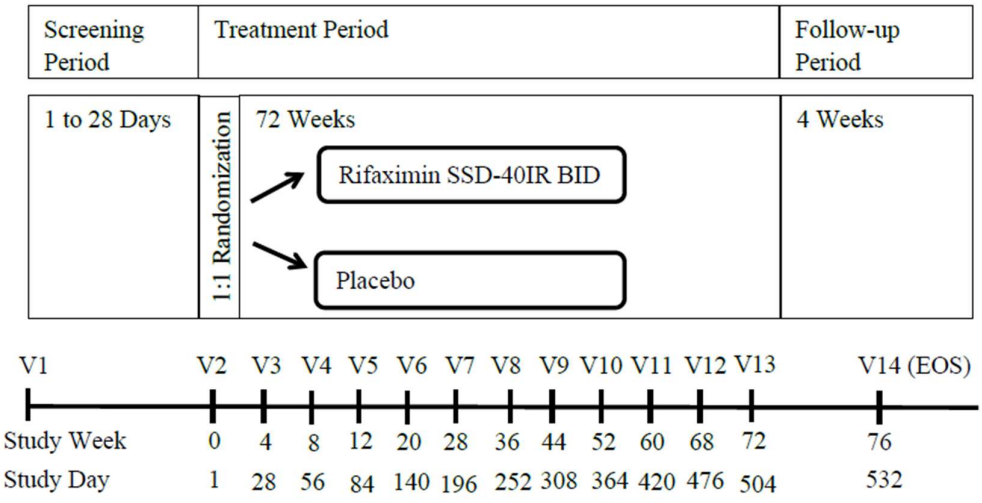
2.2.1 Study Design

This study is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of rifaximin SSD-40IR for the delay of early encephalopathy decompensation in participants with liver cirrhosis. Participants who have cirrhosis determined by histopathological evidence, transient elastography or presence of esophageal varices, and who have not previously experienced OHE, spontaneous bacterial peritonitis (SBP), esophageal variceal bleeding (EVB), or acute kidney injury hepatorenal syndrome (AKI-HRS) will be enrolled in the study.

Approximately 466 participants who successfully complete the 28-day Screening Period will enter the 72-week Treatment Period and a 4-week Follow-up period. Participants will be randomized in a 1:1 allocation to 1 of 2 treatment groups as noted in Figure 1. All treatments will be administered BID. Approximately 100 global study centers are expected to participate in the study located in North America and Australia.

Assessments of efficacy and safety will be performed during clinic visits at Weeks 0 (Day 1), 4, 8, 12, 20, 28, 36, 44, 52, 60, 68 and 72 (EOT) and during telephone calls at Weeks 16, 24, 32, 40, 48, 56 and 64. All subjects will complete an End of Study (EOS) visit at Week 76 for final safety assessments. Participants who develop OHE during the Treatment Period will be followed until the end of the 72-week trial and will be allowed access to standard of care medications to treat OHE for the remainder of the trial. If a subject prematurely discontinues treatment, every attempt will be made to obtain EOT and EOS assessments.

Figure 1 Study Schema



2.2.2 Study Treatment

Participants who meet the eligibility criteria and have given written informed consent will be randomized in a 1:1 allocation to one of two treatment groups. All treatments will be BID.

Treatment A: Rifaximin SSD-40IR BID

Treatment B: Placebo BID

2.3 Sample Size Determination

No prior data from published literature are available on the proposed primary endpoint of this study. Data on the role of rifaximin in the primary prophylaxis of SBP in patients with compensated liver cirrhosis and the treatment of patients with HE were used for sample size and power calculation, and then amended based on the expected participant population in this current study.

It is assumed that approximately 10% of rifaximin SSD-40IR subjects and 20% of placebo subjects will experience OHE over the course of 48 weeks of treatment. With two-sided type I error rate of 0.05, and dropout rate around 10%, approximately 233 subjects per treatment group will provide at least 90% power to demonstrate the superiority of rifaximin SSD-40IR to placebo using the log-rank test during the 72-week treatment period (nQuery log-rank test based on exponential survival).

3. Statistical Analysis

3.1 Data Analysis General Considerations

The final CSR analysis will be performed by SDC on all data from all participants after the study is completed and database is locked and released for unblinding. SAS® version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

The following treatment groups will be presented:

- Rifaximin SSD-40IR
- Placebo
- Total

Baseline: Defined as last available value prior to first dose of study drug for all analyses except the Time-to-Event endpoints, which will utilize Date of Randomization for the baseline.

Duration of study drug exposure is defined as the last dose of study drug – first dose of study drug +1.

In general, all data will be listed by participant and visit/time point where appropriate. The total number of participants under the stated population will be displayed in the header of the summary tables.

EOT value is defined as last available post-baseline value during the treatment period.

Unscheduled data, such as information from unscheduled visits or repeat laboratory tests, will be presented in the data listings. In general, these data will be excluded from the summary tables, with the exception of OHE events and adverse events. However, for laboratory

summaries, the first available value from unscheduled visit or retest visit after a scheduled visit will be used if the value from the scheduled visit is missing or invalid. Unscheduled visits may also be used in tables should they satisfy the End of Treatment definition; EOT assessments are defined as the last post-baseline assessments available during the Treatment Period.

All data collected in the database will be presented in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock and prior to breaking the blind. Any analyses performed subsequent to database lock or breaking the blind will be considered post hoc and exploratory. Post hoc analyses will be labelled as such in the corresponding statistical output and identified in the CSR.

In general, statistical testing will be 2-sided at the alpha=0.05 level of significance, unless indicated otherwise.

Detailed rules for imputation of missing/partially missing dates for AEs, prior/concomitant medications/procedures, and any other relevant medical history collected are provided in Section 4.1.

3.2 Analysis Sets

Analysis of the primary efficacy endpoint will be tested in ITT and PP populations using events adjudicated and confirmed to meet endpoint definitions by the Clinical Event Adjudication Committee (CEAC). The ITT analysis will be considered the primary analysis. The primary efficacy analysis also will be performed using the PP Population, as a sensitivity analysis. Secondary and exploratory efficacy analyses will be conducted using the ITT population.

The following analysis sets will be used in this study analysis.

Intent-to-treat (ITT) Set: The ITT population will include all randomized subjects who have taken at least 1 dose of study drug. The ITT population will be used for the primary efficacy analysis and will be utilized for all efficacy endpoints. Participants will be analyzed in the treatment group to which they were randomized.

Per Protocol (PP) Set: The PP population will include all ITT subjects who remained in the study through end of the randomized treatment period and who have not deviated from the protocol in any way likely to seriously affect the primary outcome of the study. Important protocol deviations which exclude the participant from the PP population will be identified prior to locking the study database. The primary efficacy analysis will be repeated using the PP Population, as a sensitivity analysis.

Participants will be eligible for the PP analysis if they complete the study or experience OHE, without noteworthy protocol deviations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the evaluation of treatment efficacy).

The PP population will include subjects in the ITT population who do not meet any of the following criteria:

- Failed any of the inclusion/exclusion criteria;
- Have taken any interfering concomitant medications (e.g., Prohibited therapy as stated in the protocol, verified by medical review)

- Received the incorrect study drug;
- Have not been compliant with the dosing regimen (i.e., Participants must take 80-120% of expected doses. The number of expected doses will be determined for each participant based on the length of their participation in the study);

Participants who discontinue from the study due to an AE related to study treatment will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol deviations.

Safety Population Set: The Safety population will include all randomized subjects who have taken at least one dose of study drug. Participants in the safety population will be analyzed according to the treatment they actually received.

Bacterial Resistance Population Set: The Bacterial Resistance Population will include all participants subjects with 1 or more stool or nasal samples taken.

Pharmacokinetics (PK) Substudy Analysis Set: The PK Population will include all participants in the PK substudy who have taken at least 1dose of study drug and have sufficient data to calculate PK parameters for rifaximin and 25-desacetyl rifaximin.

Concentration Population Set: The concentration population will include all participants that have 1 or more trough samples taken. The sparse PK sampling results from the Concentration Population will be summarized (descriptive statistics) in the CSR by nominal PK sampling time.

3.3 Descriptive Statistics

Continuous data will be summarized by treatment group using descriptive statistics (number of participants, mean, median, SD, minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequency and percent).

3.4 Endpoints

3.3.1 Primary Efficacy Endpoint

The primary efficacy variable is the time to first event of OHE requiring medical intervention in hospital/ER/ED/clinic or death.

- A thorough evaluation of the patient will be carried out to confirm the diagnosis of OHE, which will be made by a trained medical professional (e.g. MD, DO) using American Association for the Study of Liver Disease Guidelines.
- Every OHE diagnosis will be evaluated and confirmed to meet endpoint definitions by the Clinical Event Adjudication Committee (CEAC).
- Any deaths will be treated as occurrence of OHE and the time of death will be treated as time of OHE breakthrough.

3.3.2 Secondary Efficacy Endpoint

The secondary efficacy variable:

- Time to first Conn score ≥ 2 or confirmed OHE requiring medical intervention in hospital/ER/ED/clinic or death
- Time to all-cause hospitalization
- Time to first event of OHE that requires hospitalization, or all-cause death

3.3.3 Exploratory Endpoint

The following are the exploratory Endpoints

- Time to first non-OHE complication of cirrhosis, defined as any of the following events:
  - SBP, Variceal bleed, AKI-HRS
- Time to all-cause hospitalization or all-cause death
- Change from baseline in Model End-Stage Liver Disease (MELD) and Model End-Stage Liver Disease-Sodium (MELD-Na) score
- Changes in Animal Naming Test (ANT) scores
- Health-related quality of life (HRQL) using the 36-Item Short Form (SF-36) Health Survey and Patient-Reported Outcomes Measurement Information System (PROMIS)-29+2
- Time to a 1-point increase from baseline in Conn score
- Population PK parameters of rifaximin
- PK parameters for rifaximin and 25-desacetyl rifaximin on Visit 2/Day 1, Visit 3/Week 4, and Visit 12/Week 68/Last Study Visit conducted by noncompartmental analysis (PK substudy: Approximately 10 participants per treatment group will participate in serial PK sampling at selected sites. The remaining participants will have sparse PK samples collected.)
- For the bacterial resistance substudy:
  - Changes in the minimum inhibitory concentration (MIC) of rifaximin for E. *coli* in the stool from baseline at each substudy visit
  - Changes in the MIC of rifampin for S. *aureus* in the nasal passages from baseline at each substudy visit
  - Changes in the microbiota composition of the stool from baseline at each substudy visit

3.3.4 Safety Endpoint

The safety variables include the following:

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and infections
- All-cause mortality
- Clinically significant changes from baseline in clinical laboratory results

- Change from baseline in vital signs

3.5 Participant Disposition

Subject disposition will be summarized for all randomized subjects and will include the number of subjects randomized; number and percentage of subjects who completed or prematurely discontinued treatment and/or the study, classified by reasons for premature discontinuation; the number of subjects randomized at each study site; and the number and percentage of subjects who completed or discontinued treatment and/or the study at each study site. Participants withdrawn from the study will not be replaced. The reasons for premature treatment discontinuation include:

- Subject develops OHE
- Subject has a liver transplant during the study
- Subject meets the criteria for acute-on-chronic liver failure
- Occurrence of an AE and/or SAE that suggests an unacceptable risk to the subject, in the judgment of the investigator, including worsening of the disease under study
- Pregnancy

A subject may be discontinued from treatment for any of the following reasons (upon discussion with the sponsor):

- Investigator discretion
- Total bilirubin increases by ≥ 3 mg/dL over the baseline
- Direct bilirubin increases by ≥ 1.5 mg/dL over the baseline
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels increase by 2 grades from baseline according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0
- International normalized ratio (INR) increase of ≥ 1 point over the baseline (excluding participants on warfarin)

Participants whose treatment is discontinued should be followed for 72 weeks from randomization, as possible, however discontinuation from the study may be warranted for the following reasons:

- Subject request to withdraw.
- Sponsor decision to terminate the study.

  NOTE: Participants who develop HCC will continue in the study, and their data will be censored at the time of HCC diagnosis.

3.6 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment using the ITT, PP, and safety populations. Demographic characteristics include age, gender, race, ethnicity, height and weight.

Baseline characteristics include:

- MELD score and MELD-Na score (from central laboratory)
- Child-Pugh classification
- Conn score
- Liver Cirrhosis Etiology
- Time since first diagnosis of liver cirrhosis, defined as first dose date minus date of first diagnosis of liver cirrhosis + 1. Randomization date will be used if first dose date is missing
- Diabetes at Screening (Yes vs. No)
- Ascites present at Screening (Yes vs No)
- History of ascites (Yes vs No)
- MMSE Score

3.7 Measurements of Treatment Compliance and Extent of Exposure

The number of participants administered study drug and the duration of exposure to study drug will be summarized descriptively by treatment group. Duration of exposure is defined as last dose
of study drug – first dose of study drug +1.

Treatment compliance will be calculated as number of pills taken divided by number of pills expected to be taken during study participation. 80% to 120% of compliance is counted as compliant.

Calculated overall compliance will be summarized descriptively by treatment group.

3.8 Prior and Concomitant Medications

Prior and concomitant medications will be classified according to the WHO-DDE dictionary version March 2017 or later.

Prior medications are those administered within 30 days of Visit 1 (screening). Concomitant medications are those which start on or after the first day of study treatment. A medication which begins before the start of study treatment and continues into the treatment period will be considered as concomitant.

The number and percentage of subjects receiving a prior or concomitant medication will be displayed by the fourth level ATC group (Chemical subgroup), PT, and treatment group for safety population set.

Prior and concomitant medication summaries will be sorted alphabetically by generic term within ATC class, PT and treatment group.

3.9 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary and summarized descriptively by MedDRA SOC, MedDRA PT, and treatment group for safety population set.

A listing will be presented by participant and treatment group.

3.10 Protocol Deviations

A listing will be generated for inclusion/exclusion criteria violations and protocol deviations. Important protocol deviations (important protocol deviations resulting in exclusion from the Per Protocol Population) will be summarized.

3.11 Primary Objective(s) Analysis

The primary efficacy endpoint is time to first event of OHE requiring medical intervention in hospital/ER/ED/clinic or death.

3.11.1 Primary Estimand

Primary Efficacy Endpoint:

- Time to first event of OHE requiring medical intervention in hospital/ER/ED/clinic or death.
    - A thorough evaluation of the patient will be carried out to confirm the diagnosis of OHE, which will be made by a trained medical professional (e.g. MD, DO) using AASLD Guidelines.
    - Every OHE diagnosis will be adjudicated and confirmed to meet endpoint definitions by the Clinical Event Adjudication Committee (CEAC).
- Treatment:
    - Twice daily dosing, up to 72-week treatment period
    - Rifaximin SSD-40IR (BID)
    - Placebo (BID)
- Population:

  Male and non-pregnant, non-nursing females ≥ 18 and ≤ 85 years with liver cirrhosis and medically controlled ascites who have not previously experienced an episode of OHE or SBP.
- Variable:

  Time to first event of OHE requiring medical intervention in hospital/ER/ED/clinic or death.

  Diagnosis of OHE will be made by a trained medical professional (MD, DO) using AASLD Guideline. Every OHE diagnosis will be adjudicated and confirmed to meet endpoint definitions by the Clinical Event adjudication Committee (CEAC).

  Any deaths will be treated as occurrence of OHE and the time of death will be treated as time of OHE breakthrough.

- Population-level Summary:

  The population-level summary will be the comparison of survival distributions between rifaximin and placebo, where the event of interest is the first event of OHE.

- Intercurrent Events

  The following intercurrent events will be addressed in the primary analysis:

  - Discontinuation of study treatment prior to first OHE event or EOT
  - Use of additional or alternative treatment
    - Lactulose
    - Prescription rifaximin
    - Chronic daily use of Polyethylene Glycol
    - Benzodiazepine
    - New or changed psychoactive medicine regimen
    - New or changed opioid regimen
    - Antibiotic use > 14 days
  - Low compliance to the planned course of treatment

Two strategies will be used to handle the intercurrent events in the study.

The treatment policy strategy aims to answer the question: What is the treatment effect in the targeted population of subjects with liver cirrhosis regardless of treatment discontinuation, use of alternative treatment or low compliance to the planned course of treatment? The treatment policy strategy for the efficacy objectives in this study will define the primary estimand.

The hypothetical strategy aims to answer the question: What is the treatment effect in the targeted population of subjects with liver cirrhosis if all subjects had continued to use assigned treatments (with good compliance) and did not use alternative treatment? The hypothetical strategy for the efficacy objectives in this study will be used to define the secondary, or supportive, estimand.

3.11.2 Hypotheses

The null hypothesis is equal time distribution from baseline to first OHE breakthrough between rifaximin and placebo. Rejection of the null hypothesis indicates that the event rates differ between rifaximin and placebo at one or more time points during the study.

$H0: S1(t) = S2(t)$

versus the alternative:

$HA: S1(t) \neq S2(t)$

Where S1(t) and S2(t) represent the cumulative probability distributions of the times from baseline until the first OHE breakthrough for SSD-40IR and placebo arm, respectively.

3.11.3 Primary Efficacy Analysis

Diagnosis of OHE will be made by a trained medical professional (MD, DO) using AASLD Guidelines and these events will be adjudicated.

The incidence of first OHE events over the 72-week Treatment Period will be summarized by treatment group. The data will consist of count and exposure time, where the counts are the number of subjects with an OHE event as specified for the primary endpoint and the exposure times are the total time-on-study of all subjects with or without the occurrence of OHE. Each subject's contribution to the total time is stopped at the time of first occurrence of OHE. Participants who complete the entire 72-week treatment period without meeting the definition of OHE will be censored at the end of the treatment period or final visit.

The log-rank test stratified by country will be used for comparing distributions of time until the occurrence of an OHE between rifaximin and placebo arms. The likelihood of first OHE occurrence in rifaximin versus placebo will be expressed as a hazard ratio, and its associated 95% CIs. These will be estimated using a Cox proportional hazard model with country as a stratification factor.

In addition, Kaplan-Meier methods will be used to estimate the proportions of subjects experiencing an OHE episode on Days 28, 84, 140, 196, 252, 308, 364, 420, 476, etc. for each treatment group. A plot containing the Kaplan-Meier estimators of the survival curves for each treatment group will be provided.

The decision to include country as a factor in the primary (and secondary) efficacy analysis may be dependent upon the number of participants in each level of stratification. For example, if very few subjects are represented within one of the two country stratum, there may be no reason to expect any influence of this factor on the endpoints. Moreover, in this scenario, the inclusion of country in a statistical model could reduce the overall power and stability of the estimated treatment effect. Such a determination will be made upon review of the data prior to database lock; and justification for this decision will be outlined in the CSR.

3.11.4 Treatment Policy Strategy

The treatment policy strategy for the efficacy objectives in this study will define the primary estimand. For treatment policy strategy, the treatment effect will be estimated regardless of treatment discontinuation, use of alternative treatment, or low compliance to the planned course of treatment. The treatment policy analyses will use theITT Population.

Every effort will be made to follow up with subjects about the OHE status after they terminate the study. Participants who complete the entire 72-week treatment period without OHE breakthrough will be censored at the end of the treatment period. Participants who terminate early will be contacted approximately 72 weeks from Randomization to determine if they experienced the primary endpoint, and if so, when the OHE event occurred. For subjects who did not experience an OHE event, data will be censored at the time of their last visit. Participants who do not have follow-up information after treatment discontinuation will be censored at the time of their last visit/contact.

3.11.5 Hypothetical Strategy

For the hypothetical strategy, the treatment effect in the targeted population will be estimated as if all subjects had continued to use assigned treatments, did not use alternative treatment, and did not have unacceptable overall compliance. For subjects who had unacceptable overall compliance, they will be censored 90 days after the date of the study visit where compliance first fell out of acceptable limits, with any confirmed OHE occurring within 90 days of that date counted as an event in the analysis. For subjects who discontinue study treatment early, they will be censored 90 days after last dose of study medication (last dose date + 90 days), with any confirmed OHE occurring within 90 days of last dose counted as an event in the analysis. The 90-day window is based on previous studies of rifaximin 550 mg tablets three times daily in irritable bowel syndrome without constipation (Pimentel 2011); the studies showed continued effect up to 10 weeks after rifaximin treatment. It is also suggested that rifaximin effect diminishes after 10 weeks in a study of diarrhea-predominate irritable bowel syndrome (Lembo 2016). Therefore, a 90-day washout was used for prescription rifaximin for the participants enrolled into RNLC3131, and the 90-day period is similarly considered relevant for the follow-up period for participants who discontinue study drug prematurely. For subjects who use an alternative treatment for an event which is not confirmed to be OHE, they will be censored at the time when the intercurrent event occurred. Participants who complete the entire 72-week treatment period without OHE breakthrough and without alternative treatment intercurrent event will be censored at the end of the treatment period.

3.11.6 Sensitivity and Tipping Point Analyses

In addition, sensitivity analyses will be performed. Participants who terminated early (including death) or used alternative treatment will be treated as experiencing OHE breakthrough at the time of termination or starting alternative treatment (Worst Case Scenario). This worst-case scenario analysis will be repeated with events for which a determination cannot be made ('unable to evaluate'), counted as primary event OHE.

Tipping point analyses will also be conducted as additional sensitivity analyses to assess the robustness of the hypothetical strategy approach to handling treatment discontinuation. The assumptions with respect to how long after treatment discontinuation that events should be counted on the 2 treatment groups will be allowed to vary independently. Details are provided in Appendix 4.3.

Primary endpoint analyses will be repeated for the Per Protocol Population (ITT Population analysis for the subset of participants who completed the study or experienced confirmed OHE or death, without noteworthy protocol deviations as stated in Section 3.2), and Per Protocol Population using the hypothetical policy strategy for alternative treatment and treatment discontinuation (PPH Population). For the PPH Population, a participant will be excluded entirely if the participant:

- Failed any of the inclusion/exclusion criteria;
- Received the incorrect study drug;
- Was not compliant with the dosing regimen (i.e., Participants must take 80-120% of expected doses. The number of expected doses will be determined based on the length of their participation in the study);

But censored as stated above if the participant:

- Discontinued study treatment early;
- Used alternative treatment

3.12 Secondary Objective(s) Analysis

The secondary efficacy endpoints in the study are:

- Time to first Conn score ≥ 2 or confirmed OHE requiring medical intervention in hospital/ER/ED/clinic or death
- Time to all-cause hospitalization
- Time to first event of OHE that requires hospitalization, or all-cause death

The analysis will utilize the ITT population. The analysis of the time to secondary event efficacy endpoints will involve treatment group comparisons utilizing the log-rank test stratified by country. The incidence of first secondary event over the 72-week treatment period will be summarized by treatment group, similar to the primary efficacy analysis.

In addition, Kaplan-Meier methods will be used to estimate the proportions of subjects experiencing all-cause hospitalization on Days 28, 84, 140, 196, 252, 308, 364, 420, 476, etc. for each treatment group.

Hierarchical testing will be employed to control Type I error for the primary and secondary endpoints for the rifaximin versus placebo comparisons, in the order that the endpoints are stated.

Secondary endpoint analyses will be repeated for the Per Protocol Population (ITT Population analysis for the subset of participants without important protocol deviations) and Per Protocol Population using the hypothetical policy strategy.

3.13 Exploratory Objective(s) Analysis

Exploratory Endpoints

- Time to first non-OHE complication of cirrhosis, defined as any of the following events: SBP, Acute kidney injury-hepatorenal syndrome (AKI-HRS), and EVB
- Time to all-cause hospitalization or all-cause death
- Change from baseline in MELD and MELD-Na score
- Changes in Animal Naming Test scores
- Change from baseline in health-related quality of life (HRQoL) according to the 36-Item Short Form (SF-36) Health Survey and Patient-Reported Outcomes Measurement Information System (PROMIS)-29+2
    - Physical Care Component (PCS) and Mental Care Component (MCS) scores of the Short-Form 36 version 2 (SF-36v2); and
    - Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health domains in the SF-36v2

  - Physical Functioning, Anxiety, Depression, Fatigue, Sleep Disturbance, Ability to Participate in Social Roles, Pain Interference, Cognitive Function-Abilities and Pain Intensity domains in the (PROMIS)-29+2

- Time to one point increase from baseline in Conn score
- Population PK (will be addressed in a separate analysis plan)
- PK parameters for rifaximin and 25-desacetyl rifaximin on Visit 2/Day 1, Visit 3/Week 4, and Visit 12/Week 68/Last Study Visit conducted by noncompartmental analysis (PK substudy: Approximately 10 subjects per treatment group will participate in serial PK sampling at selected sites. The remaining subjects will have sparse PK samples collected.)
- For the bacterial resistance substudy:
  - Changes in the minimum inhibitory concentration (MIC) of rifaximin for E. coli in the stool from baseline at each substudy visit
  - Changes in the MIC of rifampin for S. aureus in the nasal passages from baseline at each substudy visit
  - Changes in the microbiota composition of the stool from baseline at each substudy visit (will be addressed in a separate analysis plan)

Time to first non-OHE complication of cirrhosis is defined as time from baseline to the time when first of any of the above complications (SBP, AKI- HRS, EVB) developed. The analysis of time to first non-OHE complication of cirrhosis will involve treatment group comparison utilizing the log-rank test stratified by country. The incidence of non-OHE complication of cirrhosis over the 72-week treatment period will be summarized by treatment group, similar to primary efficacy analysis.

In addition, Kaplan-Meier methods will be used to estimate the proportions of subjects experiencing non-OHE complications of cirrhosis on Days 28, 84, 140, 196, 252, 308, 336, etc. for each treatment group.

The analysis of time to first non-OHE complication of cirrhosis will be repeated for the Per Protocol Population and PPH Population.

- Change from baseline at Weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, and 72 in MELD and MELD-Na score for rifaximin SSD-40IR versus placebo will be summarized by treatment group and will be tested using ANCOVA with adjustment for baseline value and country.
- MELD score will be calculated by the central laboratory using the following formula:

  (0.957 * ln(Serum Cr mg/dL) + 0.378 * ln(Serum Bilirubin mg/dL) + 1.120 * ln(INR) + 0.643) * 10.
- MELD-Na score will be calculated by the central laboratory using the following formula:

  MELD - Na - [0.025 x MELD x (140- Na)] + 140.

The Animal Naming Test (ANT), the maximum number of animals named in 1 minute), is a validated tool that allows rapid assessment of HE (Campagna 2017). The cognitive skills required for adequate performance of the test requires intact executive function, which is impaired in HE.

Changes from baseline in ANT score will be summarized at each visit. Additionally, the number and percentage of subjects with ANT < 14 and >=14 at each visit will be summarized, as well as the shift from baseline for these categories.

The PROMIS-29+2 Profile Version 2.1 (PROPr) is used to calculate a preference score. Preference-based scores provide an overall summary of health-related quality of life on a common metric. Preference-based scores summarize multiple domains on a metric ranging from 0 (as bad as dead) to 1 (perfect or ideal health). Scores can be used in comparisons across groups and for cost-utility analyses. The profile includes all items in the PROMIS-29 Profile v2.1 plus two Cognitive Function Abilities items. T-scores from the measure can be used to calculate a preference-based score. Change in patient reported outcomes compared to baseline by scheduled visit will be provided. Change will be tested using ANCOVA with adjustment for baseline value and country. A by-subject listing will be provided.

The Short Form 36 Health Assessment (SF-36) v2 (standard, four-week recall) is a generic, validated instrument used to evaluate patient reported HRQoL in adults. The SF-36v2 questions are focused on eight health domain scales including: Physical Functioning (10 items), Role-Physical (4 items), Bodily Pain (2 items), General Health (5 item), Vitality (4 items), Social Functioning (2 items), Role-Emotional (3 items), and Mental Health (5 items). Scores from the eight domains are summarized into the PCS and MCS. The patient level SF-36v2 raw scores will be converted to aggregate scores and summary scores (i.e. PCS and MCS) and the eight individual domain scores (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) consistent with the instructions in the SF-36v2 user manual (3rd Edition) using the PRO CoRE 2.0 Smart Measurement® System Scoring Software. Additionally patient level SF-6D (derived from the SF-36v2 raw scores) will be calculated for each patient.

Change from baseline at Weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, and 72 in the summary scores (PCS and MCS) and the eight individual domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) of the SF-36v2 for rifaximin SSD-40IR versus placebo will be summarized by treatment group. Change will be tested using ANCOVA with adjustment for baseline value and country. Additionally, change in the SF-6D from baseline at Weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, and 72 for rifaximin SSD-40IR versus placebo will be summarized by treatment group. Change will be tested using ANCOVA with adjustment for baseline SF-6D value and country. Missing data will be handled consistent with the instructions in the SF-36v2 user manual (3rd Edition) using the PRO CoRE 2.0 Smart Measurement® System Scoring Software.

Time to one point increase from baseline in Conn score is defined as time from baseline to first one point increase in Conn score. The analysis of time to one point increase from baseline in Conn score will involve treatment group comparison utilizing the log-rank test stratified by country. The incidence of one point increase of Conn score over the 72-week treatment period will be summarized by treatment group, similar to primary efficacy analysis.

In addition, Kaplan-Meier methods will be used to estimate the proportions of subjects experiencing one point increase of Conn score on Days 28, 84, 140, 196, 252, 308, 336, etc. for each treatment group.

3.14 Safety Analysis

Safety population will be used for safety analysis.

Safety assessments will include the following:

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and infections
- All-cause mortality
- Clinically significant changes from baseline in clinical laboratory results
- Change from baseline in vital signs

Missing values will not be imputed for safety analysis.

3.14.1 Adverse Events

An adverse event (AE) is defined as:

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a study 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 (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, without any judgment about causality (i.e., whether or not considered related to the study product).

An AE does include the following:

- Exacerbation or worsening of a pre-existing illness including liver cirrhosis and non-OHE complications of cirrhosis.

  NOTE: OHE, including presenting symptoms are NOT considered adverse events, but primary efficacy endpoint. These events will not be unblinded or reported as suspected unexpected serious adverse reactions.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) as event terms; the condition that led to the procedure is the AE if it meets the definition of an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery; and social and/or convenience admissions).

- Symptoms associated with disease, which are consistent with the subject's usual clinical course; unless the subject experiences worsening of their symptom(s) or the symptom(s) meet the criteria for an SAE (exception is OHE and presenting symptoms).

A treatment-emergent AE (TEAE) is defined as an AE with a start date on or after the first dose of study drug, or that worsened following first administration of study drug.

If the start date (or time) of an AE is incomplete or missing, then the AE will be considered as a TEAE in each period unless a partial date (or time) or comment show it as a pre- or post-treatment event, or an on-treatment event.

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

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect in the offspring of a subject who received study product.

Important medical events that do not result in death, are not life-threatening, and/or do not require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Additionally, an adverse event meeting any of the serious outcomes previously defined above that is assessed by the investigator as resulting from study participation (regardless of relationship to study drug) should be treated as an SAE for this protocol (e.g., complications resulting from the taking of a blood sample or performance of a protocol required procedure).

All adverse events reported in the study will be listed, sorted by subject, onset date and time. Nevertheless, the analyses of the AEs will focus on the TEAEs.

Adverse events and medical history will be classified using standard MedDRA terminology Version 24.0 or higher.

The incidence of treatment-emergent AEs will be summarized for each treatment group by body system and MedDRA preferred term. If a subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE, using the most severe intensity.

As an overall summary of AEs, the following will be presented by treatment:

- Number and percentage of subjects experiencing TEAEs;
- Number and percentage of TEAEs by relationship to study treatment (i.e. related or unrelated);
- Number and percentage of TEAEs by severity (CTC grade);
- Number and percentage of subjects experiencing SAEs;

- Number and percentage of subjects experiencing study drug-related SAEs;
- TEAE/TESAEs leading to permanent treatment discontinuation;
- TEAEs/TESAEs leading to study discontinuation;
- TEAEs with an outcome of death.
- TEAEs of infection (Infections and Infestations SOC)
- TEAEs of AESI
    - All bacterial infections reported as AESI
    - All confirmed bacterial infections adjudicated by the CEAC

Subjects presenting with any AEs will be listed sorted by treatment, primary system organ class (SOC), and preferred term (PT). All SAEs and AEs leading to premature withdrawal from the study, and all deaths, will be listed.

3.14.2 Safety Laboratory Values

Planned laboratory tests include:

- **Hematology:** CBC w/Differential
- **Blood Chemistry:** Comprehensive Metabolic/Liver Panel (including albumin, ALT, AST, ALP, direct bilirubin, total bilirubin, and total serum protein). AFP will be assayed at Screening (Visit 1) only.
- **Coagulation:** PT and INR
- **EtG (Ethyl Glucuronid):** Urine
- **Urinalysis:** Routine urine analysis with microscopic examination if a urinary tract infection is suspected

Separate listings of individual data for hematology, chemistry, urinalysis will be listed by laboratory test, subject, sex, and visit. In these listings, individual data will be flagged when outside the laboratory limits.

Subject listings of abnormal on-study laboratory values will be provided. Similarly, clinically significant on-study laboratory data will be presented in a second listing.

Hematology, chemistry, and urinalysis parameters will be summarized at baseline, Weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 72 (EOT), and 76 (EOS), as well as change from baseline to each visit for numeric results. Laboratory values and changes from baseline will be summarized descriptively by treatment group (N, mean, median, SD, minimum, and maximum).

A summary of shifts from baseline to EOT will be produced for each parameter by treatment group. Shifts will be summarized by Common Terminology Criteria (CTC) grade. The number and percentage of subjects in each treatment group in each shift category from baseline to Weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 72 (EOT), and 76 (EOS) will be shown for each parameter.

3.14.3 Vital Sign Measurements

Vital signs will include blood pressure (mm Hg), heart rate (beats per minute), respiratory rate, weight and temperature. Vital signs will be summarized at baseline and at Weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 72 (EOT), and 76 (EOS), as well as changes from baseline. For each summary the n, mean, median, SD, minimum, and maximum values will be given by treatment group. Pretreatment vital signs obtained closest in time to first dose of study drug will be used for summarization and analysis of baseline and change from baseline vital signs.

3.14.4 All-cause Mortality

The incidence of all-cause death will be summarized by each treatment group. The subset of deaths determined by the CEAC to be liver disease related, will also be summarized by treatment group.

3.15 Subgroup Analysis

Subgroup analysis by age group (≤ 70 years, >70 years), sex, race (Asian/non-Asian), ethnicity (Hispanic/non-Hispanic) and baseline disease severity (MELD score [< 12 and ≥ 12 subgroups], MELDNa score [< 12 and ≥ 12 subgroups], INR (< 1.2, ≥ 1.2), MELD subgroup by INR subgroup, Conn score [0 or 1], and Child Pugh [Child Pugh A subgroup, Child Pugh B subgroup, Child Pugh C subgroup, Child Pugh B/C subgroup], and Child Pugh subgroup by age group), liver cirrhosis etiology of alcoholic liver disease (Yes/No), liver cirrhosis etiology of Nonalcoholic fatty liver disease/Nonalcoholic Steatohepatitis (Yes/No), diabetes (Yes/No), hypertension (Yes/No), hyperlipidemia (Yes/No), opioids and/or benzodiazepines use (Yes/No), lactulose use (Yes/No), and non-selective beta blocker (NSBB) use will be conducted for the primary, secondary, and selected exploratory efficacy endpoints.

Subgroup analysis will be conducted for the following:

- Time to first event of OHE requiring medical intervention in hospital/ER/ED/clinic or death
- Time to first Conn score ≥ 2 or confirmed OHE requiring medical intervention in hospital/ER/ED/clinic or death
- Time to all-cause hospitalization

  Time to first event of OHE that requires hospitalization, or all-cause death
- Time to first non-OHE complication of cirrhosis, defined as any of the following events: SBP, AKI-HRS, EVB
- All cause-mortality

If there is difference between treatment groups for the primary endpoint analysis by NSBB use, the primary analysis will be repeated with NSBB use included as a stratification variable in the time to event (log rank) model.

3.16 Handling of Dropouts or Missing Data

Missing values will not be imputed for safety analysis.

For efficacy endpoints, the strategies for handling missing data and dropouts are described in Section 3.11.

Refer to Appendices 4 for imputations of the dates for adverse events,

3.17 Interim Analysis

No interim analysis is planned for this study.

3.18 Changes/Clarifications in the Planned Analysis

The primary efficacy variable was stated in the protocol as "the time to first event of OHE requiring hospitalization". Upon feedback from the Clinical Event Adjudication Committee (CEAC), it was determined that the wording was too narrow to encompass all of the events judged by the CEAC to be confirmed OHE. Firstly, the wording excluded cases of OHE which occurred during hospitalization (that is, OHE was not diagnosed at admission, but was later diagnosed and treated during the hospital stay, after admission). Secondly, it did not cover the emergency room/emergency department cases which are confirmed to be OHE by the CEAC. Lastly, there were additional cases which required an in-clinic visit (although not the hospital or ER/ED) where medication such as lactulose and/or prescription rifaximin was prescribed for OHE/HE, which were considered by the CEAC to be confirmed OHE. To account for all of the situations which could be encountered and judged during the adjudication process to be confirmed OHE, the CEAC worksheet was updated to include the following categories:

- OHE resulting in hospitalization
- OHE occurring during hospitalization
- OHE at Emergency Room/Emergency Department Visit
- OHE requiring in-clinic medical intervention outside of hospital or ER/ED setting (for example: clinician-prescribed lactulose, prescription rifaximin, neomycin, metronidazole)

Therefore, the primary endpoint has been clarified in this SAP as "the time to first event of OHE requiring medical intervention in hospital/ER/ED/clinic or death" (i.e., any of the categories above). Analyses will be conducted for specific medical intervention settings as well, to explore robustness of results:

- OHE in hospital setting (either resulting in hospitalization or occurring during hospitalization)
- OHE in hospital/ER/ED setting (either resulting in hospitalization or occurring during hospitalization or at Emergency Room/Emergency Department Visit

The CEAC also requested to utilize likelihood definitions of OHE, to follow during their evaluation of each case, to ensure consistency and an assessment of strength of evidence presentation. The likelihood categories used in the CEAC worksheet are as follows:

Did an overt hepatic encephalopathy (OHE) event occur in the case that you reviewed?

☐Unlikely (< 25% likelihood)

☐Possible (25 to 50% likelihood)

☐Probable (>50% to 75% likelihood)

☐Highly likely (>75% likelihood)

☐Unable to evaluate; comments: _____

Overall confirmation of OHE event:

*☐Yes**

☐No

**at least Probable (>50% likelihood)*

The primary efficacy analysis will include all OHE cases judged to be at least probable OHE by the CEAC. Sensitivity analyses will also be conducted for the subset of highly likely cases and separately for cases which were deemed at least possible OHE.

The secondary efficacy variable, "Time to first Conn score ≥ 2" was modified to "Time to first Conn score ≥ 2 **or confirmed OHE requiring medical intervention in hospital/ER/ED/clinic or death**", since it was noted during the study that the Conn score is not routinely captured in the Emergency Room/Emergency Department or hospital settings, although the confirmed OHE cases occurring in these settings should be captured as OHE as well, for the purposes of this endpoint.

3.19 Pharmacokinetics Analysis

Trough concentration will be summarized descriptively on the Concentration Population for each timepoint.

For trough concentration, the descriptive summary statistics additionally comprise:

- Coefficient of variation
- Geometric mean
- Geometric coefficient of variation

For the purpose of these analyses, values below the lower limit of quantitation (LLOQ) will be imputed as the ½LLOQ of the assay. Missing PK concentrations (e.g., no sample, insufficient sample volume for analysis, no result or result not valid) will be reported in a listing and classed as "Not Reported". They will be excluded from summary statistics.

A plot of the plasma concentration over time will be presented.

4. Appendix

4.1 Imputation of dates for Treatment-Emergent Adverse Events:

Start Date	Stop Date	Action
Known	Known	Considered as a treatment-emergent adverse event (TEAE) if start date on or after the date of the first dose of investigational product (IP)

Start Date	Stop Date	Action
	Partial	Considered as a TEAE if start date on or after the date of the first dose of IP. The last day of the month and the last month (i.e., December) will be used if the stop day/month is missing.
	Missing	Considered as a TEAE if start date on or after the date of the first dose of IP
Partial, but known components show that it cannot be on or after first IP taken date	Known	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
	Partial	Not a TEAE. The first day of the month and January will be used if the start day/month is missing. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
Partial, could be on or after first IP taken date	Known	Considered as TEAE, if stop date is after first IP taken date. The first IP taken date will be used if the start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. Considered as not TEAE, if stop date is prior to first IP taken date. The first day of the month and January will be used if the start day/month is missing.
	Partial	Considered as TEAE. The first IP taken date will be used if the start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date.
Missing	Known	Considered as TEAE if stop date is on or after the date of the first dose of IP.
	Partial	The last day of the month and the last month (i.e., December) will be used if the stop day/month is missing. If the imputed stop date is on or after the first dose of IP considered as a TEAE; if the year is missing, considered as a TEAE

Start Date	Stop Date	Action
	Missing	Considered as a TEAE

4.2 Imputation of dates for Prior/Concomitant Medications Start/Stop Date:

Start Date	Stop Date	Action
Known	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.
Partial	Known	If stop date is prior to the date for the first dose of IP, considered as prior; If stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Missing	Considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
Missing	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (i.e., December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if he imputed stop date is on or after the date for the first dose of IP, considered as concomitant.

Start Date	Stop Date	Action
	Missing	Considered as concomitant.

4.3 Tipping Point Analyses

Tipping point analyses will be conducted as additional sensitivity analyses to assess the robustness of the primary analysis approach for both the treatment policy strategy and the hypothetical strategy if either or both yield statistically significant results in favor of Rifaximin.

The log-rank test stratified by country will be performed on the primary estimand and secondary estimand, with hazard ratio and p-value reported for each. The tipping point analyses for both the primary estimand and secondary estimand will be conducted as follows:

1. Non-parametric Kaplan Meier multiple imputation as described in Ruan and Gray, 2008, will be utilized to impute event times under the missing at random (MAR) assumption for subjects in the Rifaximin group who had informative censoring (ex. treatment discontinuation) through intercurrent events. The survival times and censoring will be considered competing events for the purposes of imputation using the SAS macro %SASKMI (Han J, et.al). This process will be repeated to generate a total of 1000 datasets with imputed times for informative censoring (new events). The seed in this macro will remain constant at the time of database lock and will be represented by the numeric date and time of the final run (ex. 202601041259).
2. Run the Cox proportional hazards model on each of the 1000 imputed datasets and combine the results to derive a hazard ratio.
3. Using the hazard ratio, apply a sensitivity parameter to the hazard at each event time point that represents the deviation/penalty of the Rifaximin subjects with informative censoring from their observed hazard. Conduct the log rank test on the “penalized” data.
4. Incrementally increase the deviation/penalty until the results are no longer statistically significant using the log-rank test.

5. References

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