CLINICAL RESEARCH PROTOCOL

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 (RED-C)

Protocol ID:	RNLC3131
IND Number:	153212
Clinical Phase:	3
Treatment Regimen:	Rifaximin 40 mg Soluble Solid Dispersion Immediate Release Tablets (SSD-40IR) Twice Daily Placebo Twice Daily
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Principal Investigator:	Multicenter
Original Protocol Date:	20 May 2021
Protocol Amendment # 1	23 Sep 2021
Protocol Amendment # 2	30 Mar 2022

This clinical investigation is being conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and with Good Clinical Practice, as required by the United States Code of Federal Regulations applicable to clinical studies (21CFR Parts 11, 50, 54, 56 and [312]; 42 USC 282[j]); International Council for Harmonisation Harmonised Tripartite Guideline E6(R2): GCP and E2A: Safety Data Management and applicable local regulations, including the archiving of essential documents.

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SPONSOR APPROVAL PAGE

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 (RED-C)

PROTOCOL

STUDY # RNLC3131

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INVESTIGATOR PROTOCOL AGREEMENT

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, with any future amendments, and with any other study conduct procedures provided by the sponsor, Salix Pharmaceuticals, Inc. an affiliate of Bausch Health US, LLC (Salix).
- Not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board/Ethics Committee (IRB/EC), except where necessary to eliminate an immediate hazard to the participants, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug(s), as described in this protocol and any other information provided by the sponsor including, but not limited to the following: the current Investigator's Brochure or equivalent document provided by Salix, and the approved product label, if applicable.
- That I am aware of, and will comply with, "good clinical practices" and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug(s) and of their study-related duties and functions as described in the protocol.
- To periodic on-site monitoring of the case report forms (CRFs) and source documents by Salix or designee and to on-site inspection of CRFs and source documents by appropriate regulatory authorities, including but not limited to, the United States Food and Drug Administration, local governing regulatory bodies, and IRB/EC inspectors.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or study drug, and more generally about his/her financial ties with the sponsor. Salix will use and disclose the information solely for the purpose of complying with regulatory requirements.

  Hence, I:
  - Agree to supply Salix with any information regarding ownership interest and financial ties (including those of my spouse and dependent children);
  - Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
  - Agree that Salix may disclose this information about such ownership interests and financial ties to regulatory authorities.

Investigator Name [Print]	**Investigator Signature**	**Date**

SYNOPSIS

PROTOCOL TITLE	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 (RED-C)
PROTOCOL NUMBER	RNLC3131
SPONSOR	Salix Pharmaceuticals, Inc., an affiliate of Bausch Health US, LLC
INVESTIGATIONAL PRODUCT	Rifaximin 40 mg Soluble Solid Dispersion Immediate Release Tablets (SSD-40IR) Twice Daily (BID)
OBJECTIVE	The primary objective of this study is to assess the efficacy of rifaximin SSD-40IR versus placebo to delay the occurrence of HE-related hospitalization.
TREATMENT	BID dosing; 72-week Treatment Period • Rifaximin SSD-40IR • Placebo
STUDY DESIGN	Study RNLC3131 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of rifaximin SSD-40IR for the delay of the first episode of overt hepatic encephalopathy (OHE) decompensation in advanced liver cirrhosis, defined by the presence of medically controlled ascites. 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. Participants will complete a 28-day Screening Period, a 72-week Treatment Period, and a 4-week Follow-up Period. Participants who successfully complete the Screening Period will enter the Treatment Period and will be randomized in a 1:1 allocation to 1 of 2 treatment groups as noted above. All treatments will be administered BID.
STUDY DURATION	Participant participation will be up to 80 weeks, including screening, treatment, and follow-up.
PARTICIPANT POPULATION	Male and non-pregnant, non-nursing females ≥18 and ≤70 years with liver cirrhosis and medically controlled ascites who have not previously experienced an episode of OHE, SBP, EVB, or AKI-HRS.
NUMBER OF PARTICIPANTS	Approximately 466

NUMBER OF CENTERS	Approximately 100
LOCATION	North America and Asia Pacific
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	A participant will be eligible for inclusion in this study if he/she meets all the following criteria: 1. Participant has a diagnosis of advanced liver cirrhosis with medically controlled ascites (>30 days) not requiring therapeutic paracentesis (prophylactic variceal banding allowed if no history of previous variceal bleeding). • Cirrhosis diagnosis can be made using any of the following: • Histopathological evidence of cirrhosis • Magnetic resonance imaging • Computer tomography • Fibroscan (Transient Elastography) • Imaging (sonographic or cross-sectional) • Presence of esophageal varices • Thrombocytopenia (<150,000) in chronic liver disease (CLD) 2. Participant has a Child-Pugh B Classification (score of 7 to 9 inclusive) without OHE. 3. Participant has a Conn (West Haven Criteria) score of < 2. 4. Participant has a Mini-Mental State Examination (MMSE) score ≥ 24 at screening and baseline. 5. Participant is ≥ 18 and ≤ 85 years of age. 6. Females of childbearing (reproductive) potential must have a negative serum or urine pregnancy test at screening. All participants must agree to use 2 acceptable methods of contraception throughout their participation in the study. 7. Participant must be able to independently read, fully understand and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form (ICF) without additional support and provide authorization as appropriate per local privacy regulations.

MAIN CRITERIA FOR EXCLUSION	A participant will not be eligible for inclusion in this study if any of the following criteria apply: 1. Participant has an active coronavirus disease 2019 (COVID-19) infection that is unresolved or, in the opinion of the investigator, may affect evaluation of the study drug or place the subject at undue risk. 2. Participant has a history of anaphylaxis or hypersensitivity to rifaximin, rifampin, rifamycin antimicrobial agents, or any of the components of rifaximin. 3. Participant has a history of SBP, primary or secondary SBP prophylaxis, EVB, or AKI-HRS. • AKI-HRS diagnostic criteria: ≥ Stage 2 AKI; no improvement of serum creatinine after ≥ 48 hours of diuretic withdrawal and volume expansion with albumin at a dose of 1 g/kg of body weight, up to a maximum of 100 g daily; absence of hypovolemic shock or infection that require vasoactive drugs to support blood pressure; no current or recent use of nephrotoxic drugs; proteinuria < 500 mg/day, and hematuria <50 RBC/high power field**.** 4. a. Participant has a documented history of an OHE episode (Conn score ≥ 2). b. Participant has a history of rifaximin 550 mg and lactulose use for suspected OHE episode. Short course (≤ 2 weeks) of rifaximin for non-OHE indications (e.g., Traveler's Diarrhea or Irritable Bowel Syndrome with Diarrhea indications), > 90 days prior to screening is allowed. Occasional and intermittent use of lactulose (≤ 2 weeks) for non-OHE indications (e.g., constipation or for testing purposes, like lactulose breath test), > 1 weeks prior to screening is allowed. 5. Participant has uncontrolled neurological or psychiatric conditions which may confound the assessment of cognitive function (e.g., dementia, schizophrenia, etc.). Participants with generalized seizure within 30 days prior to screening are excluded.

	6. Participants with focal neurological deficits due to a neurological event such as cerebrovascular accident. 7. Participants with Wernicke's or Wernicke-Korsakoff encephalopathy. 8. Participant has pseudomembranous colitis, abdominal abscess, or clinically significant strictures and fistulas of the gastrointestinal tract. 9. Participant consumes more than moderate amounts of alcohol, defined as 1 standard drink per day for women and 2 standard drinks per day for men. 10. Participant has a history of substance abuse < 6 months prior to signing the ICF and cannot refrain from substance abuse during the study period. For alcohol abuse, participants undergoing alcohol use counseling or receiving Alcohol Use Disorder pharmacotherapy, can be considered for inclusion. 11. Participants on antipsychotic medications should be excluded irrespective of indication or dose. Benzodiazepine, psychoactive medicine, and opioid use are excluded, with the exception of: a. Participants on psychoactive medications with a washout period of 30 days before providing consent. Participants on stable and low-dose psychoactive medicines, may be included, as well as participants on stable low dose of short-acting benzodiazepines, taken at night and not for more than 3 nights per week, for the last 2 weeks. b. Participants are allowed on a stable opioid dose, where the total chronic and breakthrough (pro re nata [PRN]) doses do not exceed 100 milligrams morphine equivalents (MME), for at least 2 weeks, with 3 or more satisfactory bowel movements per week in the last 2 weeks without the aid of laxatives or on stable dose of laxatives. 12. Participant is currently taking Warfarin that cannot be discontinued. If there is a washout period of 7 days or more before informed consent for participants taking Warfarin, they may be included.

	13. Participant has been diagnosed with an uncontrolled infection < 4 weeks prior to screening. 14. Participant has been diagnosed with an upper gastrointestinal bleed from non-variceal sources < 6 weeks prior to screening. 15. Participant shows the presence of intestinal obstruction or has inflammatory bowel disease. 16. Participant has undergone bariatric surgery or intestinal resection. Limited segmental resection of colon (e.g., adenomatous polyp) > 2 years prior is allowed. 17. Participant has a history of portal vein thrombosis, a history of a transjugular intrahepatic portosystemic shunt (TIPS) procedure, or plans to undergo a TIPS procedure. 18. Participant has a history of shunt surgery or direct intrahepatic portocaval shunt (DIPS) procedure for portal hypertension or plans to undergo a DIPS procedure. 19. Participant requires peritoneal dialysis or hemodialysis. 20. Participant has undergone prophylactic variceal banding within 2 weeks of screening or is scheduled to undergo prophylactic variceal banding during the study (Note: participants with previous prophylactic variceal banding will be allowed to participate in the study). 21. Participant has Type 1 or Type 2 diabetes that is not adequately controlled in the opinion of the investigator. 22. Participant has severe co-morbid disease with a life expectancy < 1 year. 23. Participant has active malignancy (except basal carcinoma of the skin), including active hepatocellular carcinoma (HCC) and/or a past history of HCC. Participants with resections or ablations of squamous cell carcinoma of the skin, or in situ carcinoma of the cervix, that occurred greater than 6 months prior to screening and are considered disease free are eligible for enrollment. 24. Evidence of HCC or a lesion suspicious for HCC <u>within 6 months</u> on ultrasound or contrast multiphase magnetic resonance imaging (MRI) or computed tomography (CT). If this imaging is not available, or if alpha-fetoprotein (AFP) ≥ 20 ng/ml at screening, participants should undergo standard

	of care diagnostic procedures with their personal physician to rule out HCC during the screening period. 25. Participant has any condition or circumstance that adversely affects the participant, could cause noncompliance with treatment or visits, may impact the interpretation of clinical data, could cause bias, or may otherwise contraindicate the participant's participation in the study. 26. Participant used any investigational product or device within 30 days or 5 half-lives of the investigational product (whichever comes first) of providing consent.

CONCOMITANT THERAPY	All prior medications administered within 30 days of screening and all concomitant medications (CMs) will be recorded in the participant's medical record and on the CM page of the electronic case report form (eCRF). Prohibited Therapy: • Non-study rifaximin (e.g., commercial rifaximin, Xifaxan® 550 mg tablets), rifampin or other rifamycin derivatives are prohibited within 90 days of providing consent, and throughout the study. • Use of Warfarin within 7 days of providing informed consent, and throughout the study. • Lactulose/lactitol, neomycin, metronidazole, pre/probiotic capsules, L-ornithine-L-aspartate, or branched chain amino acids within 30 days of providing consent, and throughout the study. Occasional and intermittent use of lactulose (≤ 2 weeks) for non-OHE indications (e.g., constipation or for testing purposes, like lactulose breath test), > 1 weeks prior to screening is allowed. Fecal or intestinal microbiota transplantation during the study and within 1 year of providing consent, are prohibited. • Participants on antipsychotic medications should be excluded irrespective of indication or dose. Benzodiazepine, psychoactive medicine, and opioid use are excluded, with the exception of: o Participants on psychoactive medications with a washout period of 30 days before providing consent. Participants on stable and low-dose psychoactive medicines, may be included, as well as participants on stable low dose of short-acting benzodiazepines, taken at night and not for more than 3 nights per week, for the last 2 weeks. o Participants are allowed on a stable opioid dose, where the total chronic and breakthrough (PRN) doses do not exceed 100 MME, for at least 2 weeks, with 3 or more satisfactory bowel movements per week in the last 2 weeks without the aid of laxatives or on stable dose of laxatives. • Chronic antibiotic use throughout the study is prohibited. A short-course of antibiotic therapy (≤ 10 days; non-rifamycin

	and non-quinolone classes only) to treat non-cirrhosis-related conditions such as sinusitis, dental therapy prophylaxis, urinary tract infections, etc. is permitted. Longer courses of therapy will require the permission of the sponsor. • Investigational drug use within 30 days of providing consent, and throughout the study. • Gabapentin and pregabalin are prohibited throughout the study.
EFFICACY ENDPOINTS	Primary Efficacy Endpoint: • Time to first event of OHE requiring hospitalization o 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. o Every OHE diagnosis will be evaluated and confirmed to meet endpoint definitions by the Clinical Event Adjudication Committee (CEAC). Secondary Efficacy Endpoint: • Time to all-cause hospitalization Exploratory Endpoints • Time to first non-OHE complication of cirrhosis, defined as any of the following events: o SBP, Variceal bleed, AKI-HRS • Time to first event of OHE that requires 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 scores • Health-related quality of life (HRQL) using the 36-Item Short Form (SF-36) Health Survey • Change from baseline in Caregiver Reported Burden • 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.)
SAFETY ENDPOINTS	The safety endpoints are as follows: • 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.
SAMPLE SIZE	Approximately 466 participants (233 per arm) will be randomized in a 1:1 ratio to receive either rifaximin SSD-40IR or placebo. It is assumed that approximately 10% of rifaximin SSD-40IR participants and 20% of placebo participants will experience OHE over the course of 48 weeks of treatment (hazard ratio of 0.472). With 2-sided Type I error rate of 0.05, and dropout rate around 10%, approximately 233 participants 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).
STATISTICAL METHODOLOGY	The primary efficacy analysis, comparing the time to first OHE event requiring hospitalization for the rifaximin SSD-40IR and placebo groups will be tested using the log-rank test stratified by country. Analysis of primary efficacy endpoint will be tested in the Intent-to-Treat (ITT) and Per-Protocol (PP) populations using events adjudicated and confirmed to meet endpoint definitions by the CEAC. The ITT analysis will be considered the primary analysis. The primary efficacy analysis also will be performed on the PP Population as a sensitivity analysis. • The ITT Population will include all randomized participants who have taken at least 1 dose of study drug.

	• The PP Population will include all ITT participants 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 will be identified prior to locking the study database. • The Safety Population will include all randomized participants who have taken at least 1 dose of study drug. The incidence of TEAEs will be summarized for each treatment group by body system and by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. If a participant reports the same adverse event (AE) more than once, then that participant will only be counted once for the summary of that AE, using the most severe intensity. Noncompartmental analysis (NCA) will be conducted for participants in the PK substudy using intensive PK samples collected at Visit 2/Day 1, Visit 3/Week 4, Visit 8/Week 36, and Visit 12/Week 68/Last Study Visit. Rifaximin and 25-desacetyl rifaximin PK parameters to be calculated include maximum plasma concentration (C_{max}), time to C_{max}, and area under the plasma concentration-time curve from time 0 to 8 hours post-dose. PK will be summarized using descriptive statistics, including number of observations, mean, median, percent coefficient of variation, standard deviation, minimum, and maximum.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACLF	Acute-on-chronic liver failure
ADL	Activity of daily living
AE	Adverse event
AESI	Adverse event of special interest
AFP	Alpha-fetoprotein
AKI	Acute kidney injury
AKI-HRS	Acute kidney injury-hepatorenal syndrome
ALT	Alanine aminotransferase
ANT	Animal Naming Test
AST	Aspartate aminotransferase
BID	Twice daily
CCS	Croscarmellose sodium
CEAC	Clinical Event Adjudication Committee
CI	Confidence interval
CLD	Chronic liver disease
CM	Concomitant medication
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DIPS	Direct intrahepatic portocaval shunt
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of study
EOT	End of treatment
EtG	Ethyl glucuronide
EVB	Esophageal variceal bleeding

Abbreviation	Definition
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HCC	Hepatocellular carcinoma
HE	Hepatic encephalopathy
HEGI	Hepatic Encephalopathy Grading Instrument
HRS	Hepatorenal syndrome
HRQL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio
IR	Immediate release
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model End-Stage Liver Disease
MELD-Na	Model End-Stage Liver Disease-Sodium
MME	Milligrams morphine equivalents
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
OHE	Overt hepatic encephalopathy
P-gp	P-glycoprotein
PHI	Protected health information
PK	Pharmacokinetic(s)
PP	Per-Protocol
PRN	Pro re nata
PT	Preferred term (also prothrombin time)
QHS	Once daily at bedtime
RED-C	Rifaximin for Encephalopathy Decompensation in Cirrhosis
SAE	Serious adverse event
SBP	Spontaneous bacterial peritonitis
SD	Standard deviation

Abbreviation	Definition
SER	Sustained extended release
SF-36	36-Item Short Form Health Survey
SOC	System organ class
SSD	Soluble Solid Dispersion
TC	Telephone call
TEAE	Treatment-emergent adverse event
TIPS	Transjugular intrahepatic portosystemic shunt
ULN	Upper limit of normal
US	United States
WHC	West Haven Criteria

1.0 INTRODUCTION

1.1 Disease Background and Scientific Rationale

The magnitude of the health care burden caused by liver disease in the United States (US) is significant from both a societal and health economic perspective. Approximately 4.5 million people have liver disease in the US (National Center for Health Statistics, 2018). In 2004, 2.3 million ambulatory care visits, and 759,000 hospitalizations were needed to care for these patients (Everhardt, 2008). Cirrhosis is a major cause of much of the chronic liver disease (CLD) in the US and is the 12th leading cause of death. Using data from the Nationwide Inpatient Sample database from 1998 to 2006, a series of 217,948 hospital admissions with a primary diagnosis of cirrhosis was evaluated. Mortality rates from complications of cirrhosis in this series were approximately 8%, 18%, 10%, and 45% for ascites, hepatic encephalopathy (HE), variceal bleeding, and hepatorenal syndrome (HRS), respectively(Singla 2011). Similarly, other studies have demonstrated that the in-hospital mortality of patients with spontaneous bacterial peritonitis (SBP) ranges from 10-50% (Toledo, 1993; Runyon, 1991; Rimola, 1995; Felisart, 1985; Navasa, 2013; Gines, 1990; Tito, 1988; Planas, 2004).

HE is a reversible neuropsychiatric abnormality that presents in 30-45% of patients with cirrhosis (Poordad, 2007; Amodio, 2001; Guevara, 2009) and in 10-50% of patients with a transjugular intrahepatic portosystemic shunt (TIPS) (Amodio, 2001). Alterations in the production, metabolism, and excretion of nitrogenous compounds, including ammonia, contribute to the pathogenesis of HE. Other gut-derived neurotoxins, including mercaptans, phenols, manganese, short chain fatty acids, and bilirubin have also been implicated in the pathogenesis of HE. Precipitating factors for HE includes gastrointestinal bleeding, dehydration, excess dietary protein intake, hypokalemic alkalosis, infection, and constipation.

1.2 Current Therapy for Hepatic Encephalopathy

HE presents in 30-45% of patients with cirrhosis, and in 10-50% of patients with a TIPS procedure despite available treatments. Management of patients with chronic HE includes provision of supportive care, identification and removal of precipitating factors, and reduction of nitrogenous load from the gut (Romero-Gomez, 2010; Zafirova, 2010; Wright, 2007). Until 2010, lactulose was the only approved therapy for the treatment and prevention of HE in the US. Lactulose is a cathartic that is thought to lower plasma levels of ammonia by acidification of stools and purging to increase the fecal excretion of nitrogen. There is no fixed recommended dose; the dose is self-titrated by the patient to produce 2-3 soft stools per day to achieve efficacy (Product Information for Lactulose Solution, 2015). Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy (i.e., HE). While deemed effective (Sharma, 2009), the side effects of lactulose therapy include bloating, abdominal cramps, diarrhea, and an unpleasant taste; these side effects are not well tolerated and cause poor adherence to long-term treatment. It is important to note that in patients with underlying advanced liver disease, complications such as dehydration and electrolyte disturbances (e.g., hypokalemia) may

occur due to lactulose use for which other specific therapy may be required. Furthermore, lactulose can induce diarrhea, a precipitating factor of HE (Product Information for Lactulose Solution, 2015; Kalaitzakis, 2006; Bajaj, 2010; Bass, 1981; Kalaitzakis, 2007).

The mode of action of antibiotics for the treatment of HE is to reduce the number of deaminating bacteria and urease producing bacteria, thereby reducing the production of ammonia and other potential toxins. Antibiotics such as neomycin, metronidazole, and rifaximin have demonstrated efficacy and have been used with or without lactulose.

Neomycin sulfate is an aminoglycoside antibiotic that is approved for acute treatment as adjunctive therapy in hepatic coma at total daily doses of 4 to 12 grams. However, neomycin use is only recommended for short-term therapy in the treatment of HE due to the risk of nephrotoxicity and ototoxicity (Product Information for Neo-Fradin®, 2005; Strauss, 1992). Although oral neomycin is commonly considered a non-absorbed antibiotic, it has significant oral absorption (approximately 3%) and systemic exposure, especially in patients with renal insufficiency. Neomycin accumulates in soft tissues after repeated dosing, particularly in the renal cortex and inner ear. It is effective primarily against Gram-negative bacilli with some activity against Gram-positive organisms, and no activity against anaerobic bowel flora (Product Information for Neo-Fradin®, 2005; Strauss, 1992). Mainly due to these limitations, neomycin is a poor choice for long-term therapy.

Since Gram-negative anaerobic bacteria are major contributors to ammonia generation in the gut, metronidazole, an antibiotic effective against anaerobic bacteria has been considered and used in the treatment of HE (Morgan, 1982). However, metronidazole is not approved for the treatment of HE and is not recommended for long-term treatment due to central nervous system toxicity, risk of convulsive seizures and peripheral neuropathy; particularly in patients with severe hepatic disease (Product Information for FLAGYL® metronidazole tablets, 2010).

1.3 Scientific Rationale for the use of Rifaximin in Preventing Major Complications of Liver Cirrhosis

The efficacy of rifaximin in the treatment of recurrent episodes of HE was demonstrated in a randomized double-blind placebo-controlled multicenter trial of 299 participants with cirrhosis (Bass, 2010). This 6-month study enrolled participants in remission from recurrent HE, (history of ≥ 2 HE episodes with severity of Conn 2 or greater) and demonstrated that rifaximin significantly reduced the risk of an episode of HE, as compared with placebo, (hazard ratio with rifaximin, 0.42; 95% confidence interval [CI], 0.28 to 0.64; P<0.001). Further, significantly fewer participants in the rifaximin group had a hospitalization involving HE, as compared with placebo group; hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P=0.01). Rifaximin maintained remission from HE more effectively than placebo. Rifaximin 550 mg twice daily (BID) was approved by the US Food and Drug Administration (FDA) in March 2010 for the reduction in risk of recurrent overt hepatic encephalopathy (OHE).

Treatment with rifaximin maintains remission from HE more effectively than placebo over a 6-month period, and significantly reduces the risk of hospitalization involving HE. In an open-label, treatment-extension study, the long-term safety of rifaximin was evaluated in 322 adults with cirrhosis and recurrent HE receiving rifaximin 550 mg BID for at least 24 months. Median exposure for both studies was 427 days (range 2-1427 days), with 510 person-exposure years. Data from this open-label study demonstrated that continuous therapy with rifaximin affords prolonged protection from HE recurrences with decreased HE-related and all-cause hospitalizations without an increased rate of adverse events (AEs) or decreased survival. In addition, the overall rates of infection, antibiotic use, and other complications of cirrhosis such as ascites were either lower or remained stable (Mullen 2014; Vlachogiannakos, 2013).

1.4 Study Rationale

Rifaximin 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 will be conducted to assess the viability of rifaximin SSD-40IR to delay encephalopathy decompensation.

Clinical Experience with Rifaximin Soluble Solid Dispersion Tablets

While the currently marketed formulation of rifaximin has shown efficacy and safety in preventing recurrent OHE, Salix has developed a soluble solid dispersion (SSD) formulation that is water soluble, as opposed to requiring bile acids for solubility, and hence may be effective at a substantially lower dose. In addition, the lack of the necessity for bile acids is particularly appropriate in participants with hepatic dysfunction, as these patients produce less bile. The pharmacokinetics (PK) of rifaximin (SSD) were evaluated in four Phase 1 studies and two Phase 2 studies after administration of the rifaximin (SSD) immediate release (IR) formulation in either healthy volunteers or participants with impaired liver function.

Study RFPK1042 was a 2-part study evaluating the PK of rifaximin SSD at different doses and the regional absorption and bioavailability of rifaximin following targeted release at prespecified

locations in the gastrointestinal tract. Study RNPK1002 evaluated the PK of the 80 mg rifaximin SSD tablet using 3 different release formulations. Study RNDI1005 is a drug-drug interaction study that evaluated whether esomeprazole, which raises GI pH, alters the PK of the IR and sustained extended release (SER) formulation of rifaximin when administered concomitantly. Study RNPK1003 evaluated the single-dose PK of rifaximin 80 mg IR and 80 mg SER dispersion tables, as well as 80-mg and 80-mg SER administered together in participants with mild, moderate, and severe hepatic impairment and in healthy participants. Study RNLC2131 evaluated the population PK of rifaximin SSD tablets in participants with liver cirrhosis who participated in the randomized, double-blind, placebo-controlled, dose-ranging, multicenter study to assess the efficacy and safety of rifaximin SSD tablets for the prevention of complications in participants with early decompensated liver cirrhosis.

Overall, the results of the early Phase 1 studies demonstrated the safety and formulation performance of rifaximin SSD. Progressive decreases in systemic exposure as a function of increasing delays in intestinal release were observed for rifaximin SSD tablets.

Mean C_{max} values ranged from 1.41 ng/mL to 5.20 ng/mL (for the SER and IR formulations, respectively); corresponding mean area under the concentration-time curve from time 0 to theoretical infinity values were 10.2 ng·h/mL and 24.9 ng·h/mL (RNPK1002 Clinical Study Report, Table 6). Median T_{max} values were 2.0 and 1.5 hours and mean half-lives was 6.6 and 8.7 hours. Compared with the current 550 mg tablet formulation, rifaximin IR tablet formulation provides similar or lower C_{max} and area under the plasma concentration-time curve values systemically, accompanied by prolonged half-lives that may indicate increased GI residence times.

Study RNLC2131, A Phase 2 Program

Study RNLC2131 was a Phase 2, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy (prevention of hospitalization for complications of liver cirrhosis or all-cause mortality in participants with early decompensation) and safety of rifaximin SSD tablets in participants with early decompensated liver cirrhosis. Participants with documented medically non-refractory ascites who had not previously experienced SBP, EVB, or HRS were enrolled in the study. Participants completed a 1 to 21-day Screening Period, a 24-week Treatment Period, and a 2-week Follow-up Period. A total of 518 participants who successfully completed the Screening Period entered the Treatment Period and were randomized in a 1:1:1:1:1:1 allocation to 1 of 6 treatment groups. All treatments were administered once daily at bedtime (QHS).

Participants were treated QHS with rifaximin SSD, 40 mg or 80 mg tablets, in 1 of 2 formulations of IR and SER.

The active treatment groups were as follows:

- Treatment A: rifaximin SSD 40 mg QHS (IR tablet)
- Treatment B: rifaximin SSD 80 mg QHS (IR tablet)

- Treatment C: rifaximin SSD 40 mg QHS (SER tablet)
- Treatment D: rifaximin SSD 80 mg QHS (SER tablet)
- Treatment E: rifaximin SSD 80 mg (IR tablet) and SSD 80 mg (SER tablet) QHS

Overall, the mean Model End-Stage Liver Disease (MELD) score was 11.5, with the majority of participants (280 participants; 54.3%) scoring between 11 and 18. The overall mean Model End-Stage Liver Disease-Sodium (MELD-Na) score was 12.9, with the majority of participants (327 participants; 63.4%) again scoring between 11 and 18. Most participants (416 participants; 80.6%) had a class B Child-Pugh classification and a Conn score category of 0 (317 participants; 61.4%). The mean time since first diagnosis of liver cirrhosis score was 1665.5 days.

Hepatitis C was the most common liver cirrhosis etiologic category (242 participants; 46.9%) with "alcoholic liver disease" reported as the second most common (220 participants; 42.6%). The majority of participants did not have HE or diabetes at screening (364 participants; 70.5%). In general, the balance in baseline disease characteristics across all 6 treatment groups was consistent.

The primary objective of this study was to assess the efficacy of rifaximin SSD versus placebo in preventing complications of liver cirrhosis and all-cause mortality in participants with early liver decompensation.

Treatment with rifaximin IR and SER SSD was shown to be safe and well tolerated and demonstrated potential therapeutic utility, particularly the IR 40 mg QHS and SER 80 mg QHS formulas, in preventing complications of liver cirrhosis and all-cause mortality in patients with early liver decompensation.

While the primary analysis did not demonstrate statistically significant differences in time to composite endpoint of hospitalization for the liver cirrhosis complications or mortality up to 24 weeks for the combined rifaximin SSD groups versus placebo (P=0.8062) or any pairwise comparison, in a post-hoc analyses there was a consistent pattern of benefit with rifaximin SSD IR 40 mg and SSD SER 80 mg.

The IR 40 mg group post-hoc analysis revealed a statistically significant difference versus placebo (P=0.0297) for the composite endpoint of all-cause hospitalization/all-cause mortality (primary endpoint of the study was hospitalization for any of the liver cirrhosis complications (HE, EVB, SBP, or HRS) (RNLC2131 Clinical Study Report [CSR] Appendix 16.1.13). In addition, participants in the alcohol-induced only subgroup had a statistically significant difference in time to all-cause hospitalization/all-cause mortality versus placebo when treated with rifaximin IR 40 mg QHS (P=0.0298). Furthermore, participants with a Conn score of 0 demonstrated a statistically significant difference for both the overall treatment comparison of any rifaximin SSD treatment versus placebo and predominantly in favor of the IR 40 mg formulation.

Results of the sensitivity analysis on the Per-Protocol (PP) Population demonstrated a statistically significant difference in the time to hospitalization for any of the liver cirrhosis complications or

all-cause mortality up to 24 weeks that was in favor of the SER 80 mg QHS treatment group versus placebo (P=0.0464). Based on the Kaplan-Meier estimates, the SER 80 mg QHS group presented with the highest survival rate of all treatment groups for Time to Hospitalization for Any of the Liver Cirrhosis Complications by Treatment Group, however this effect was not statistically significant.

A trend was observed in the time to hospitalization for any of the liver cirrhosis complications or all-cause mortality during the 24-week period within the ≥ 947 days subgroup in favor of the SER 80 mg QHS group versus placebo (stratified log-rank P=0.0517). In addition, participants in the alcohol-induced only subgroup had a statistically significant difference in time to all-cause hospitalization/all-cause mortality versus placebo when treated with rifaximin SER 80 mg QHS P=0.0166).

The safety outcomes were consistent with the known safety profile of rifaximin. Treatment-emergent AEs (TEAEs), serious adverse events (SAEs), severe TEAEs, and drug-related TEAEs occurred most frequently in the GI disorder System Organ Class (SOC).

HE was the most common preferred term (PT) followed by ascites, edema peripheral, and diarrhea. No deaths were related to study drug. Overall, there were no clinically relevant differences observed at SOC and PT levels between groups.

Study RNHE2041, A Phase 2 Program

Study RNHE2041 was a Phase 2, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of rifaximin SSD tablets (40 mg IR and 80 mg SER) plus lactulose in participants hospitalized with OHE. Participants who had liver cirrhosis and OHE, defined as a score of 2 or 3 on the Hepatic Encephalopathy Grading Instrument (HEGI), were eligible for enrollment. Eligible participants entered the treatment period and were randomized in a 1:1:1:1:1 ratio into 1 of 5 treatment groups.

The active treatment groups were as follows:

- Treatment A: 40 mg IR rifaximin SSD tablet (SSD-40IR) once daily (QD) and lactulose
- Treatment B: 40 mg IR rifaximin SSD tablet (SSD-40IR) BID and lactulose
- Treatment C: 80 mg SER rifaximin SSD tablet (SSD-80SER) QD and lactulose
- Treatment D: 80 mg SER rifaximin SSD tablet (SSD-80SER) BID and lactulose
- Treatment E: SSD placebo tablet BID and lactulose

The blinded treatment period started upon randomization following hospital admission. Participants were on blinded treatment for up to 14 days. All participants who completed the blinded randomized treatment phase (defined as confirmed resolution of OHE), continued on to the safety Follow-up Period and received 30 days of open-label treatment with Xifaxan® 550 mg

upon hospital discharge, regardless of the treatment arm to which they were previously randomized. If a participant remained hospitalized following OHE resolution, standard of care treatment (which may have included Xifaxan® 550 mg) was given until hospital discharge. Open-label drug was only dispensed to participants upon hospital discharge.

Approximately 325 participants (65 participants per treatment arm) were planned for enrollment. An interim analysis was completed earlier than planned due to the coronavirus disease 2019 (COVID-19) pandemic.

The interim analysis was completed after enrollment of 71 of the planned 325 participants. For the primary endpoint, compared with the placebo arm, the rifaximin SSD-40IR BID arm showed a significant decrease in time to OHE resolution (p=0.0208). Additionally, a significant decrease in time to OHE resolution (p=0.0166) was shown when the SSD-40IR arms (QD plus BID) were combined.

Of the secondary endpoints, compared with the placebo arm, the rifaximin SSD-40IR BID arm and the combined SSD-40IR arms (QD plus BID) showed a reduction in time to 1-grade decrease in HEGI score (p=0.0379 and p=0.0514, respectively). None of the other findings for secondary endpoints were statistically significant.

Given the positive findings at the interim and the challenges of the pandemic, the decision was made not to continue the study to full enrollment.

Treatment with rifaximin SSD (SSD-40IR or SSD-80SER) was generally well tolerated. No unexpected TEAEs were noted. None of the TEAEs or SAEs reported in either the Randomized Treatment Phase or the Open-label Phase were considered related to study treatment.

1.5 Summary of Potential Risks and Benefits to Treatment

The safety of rifaximin has been established through experience in clinical studies for multiple indications with over 6000 participants, as well as extensive worldwide post-marketing exposure (25+ years). Salix-sponsored rifaximin studies with the marketed tablet have included HE participants who have advanced liver disease (N = 719), irritable bowel syndrome participants (N = 1930), travelers' diarrhea participants (N = 2230), and healthy volunteers in clinical pharmacology trials (N > 250). Analysis of the extensive rifaximin safety database supports the use of rifaximin in the liver cirrhosis patient population.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objective

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.

2.2 Endpoints

2.2.1 Efficacy Endpoints

2.2.1.1 Primary Efficacy Estimand

Time to first event of OHE requiring hospitalization

- Treatment:
    - BID dosing, 72-week Treatment Period
    - Rifaximin SSD-40IR (BID)
    - Placebo (BID)
- Population:

  Male and Non-pregnant, non-nursing females ≥18 and ≤70 years with liver cirrhosis and medically controlled ascites who have not previously experienced an episode of OHE, SBP, EVB, or acute kidney injury-hepatorenal syndrome (AKI-HRS).

- Variable:

  Time to first event of OHE requiring hospitalization. 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 (including the detection of disorientation [time and place] and asterixis). Every OHE diagnosis will be evaluated and confirmed to meet endpoint definitions by the Clinical Event Adjudication Committee (CEAC).

- Population-level Summary:

  The population-level summary will be the difference between rifaximin and placebo in median time to 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 End of Treatment (EOT)
  - Use of additional or alternative treatment
  - Death unrelated to underlying liver cirrhosis or OHE
  - 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 participants with liver cirrhosis regardless of treatment discontinuation, use of alternative treatment or low compliance to the planned course of treatment? The treatment policy estimand for the efficacy objectives in this study will be the primary estimand.

The hypothetical strategy aims to answer the question: What is the treatment effect in the targeted population of participants with liver cirrhosis if all participants had continued to use assigned treatments and did not use alternative treatment? The hypothetical strategy for the efficacy objectives in this study will be the secondary estimand.

Any deaths related to underlying liver cirrhosis will be treated as occurrence of OHE and the time of death will be treated as time of OHE breakthrough. Any deaths unrelated to underlying liver cirrhosis will be censored at the time of death.

2.2.1.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint of this study is:

- Time to all-cause hospitalization

2.2.1.3 Exploratory Endpoints

The exploratory endpoints of this study are:

- Time to first non-OHE complication of cirrhosis, defined as any of the following events:
  - SBP, variceal bleed, AKI-HRS
- Change from baseline in MELD and MELD-Na score
- Time to first event of OHE that requires hospitalization, or all-cause death
- Changes in Animal Naming Test (ANT) scores
- Health-related quality of life (HRQL) using the 36-Item Short Form (SF-36) Health Survey
- Change from baseline in Caregiver Reported Burden
- 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.)

2.2.2 Safety Endpoints

The safety endpoints are the following:

- Incidence of TEAEs, SAEs, and infections
- All-cause mortality
- Clinically significant changes from baseline in clinical laboratory results
- Changes from baseline in vital signs

3.0 INVESTIGATIONAL PLAN

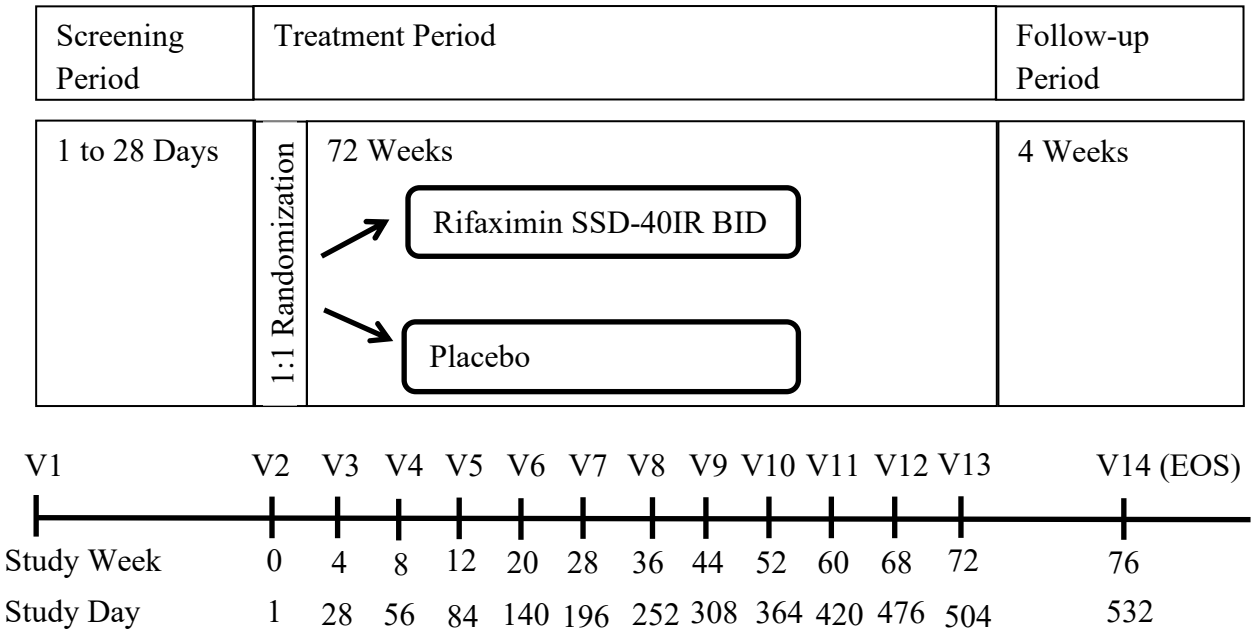
3.1 Overview of Study Design

This 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 advanced liver cirrhosis. Approximately 466 participants who successfully complete the Screening Period will enter the Treatment Period and 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.

Objectives and endpoints for the study are provided Section 2.0. Assessments of efficacy and safety (Appendix 1; Section 6) 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 participants 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 participant prematurely discontinues study treatment, every attempt will be made to obtain EOT and EOS assessments and the participant should be followed until the end of the 72-week trial.

Participants and caregivers should be given instructions on what to do if the patient exhibits unusual behavior consistent with suspected OHE. Per the protocol, such participants should go immediately to their local emergency department (or an emergency department pre-determined with the investigator), and if possible, notify the emergency department physician of their current participation in a clinical trial.

Figure 1. Study Schema



3.2 Treatment Assignment/Randomization

Participants who meet the eligibility criteria and have given written informed consent will be randomized in a 1:1 allocation to 1 of 2 treatment groups. All treatments will be BID.

- Treatment A:Rifaximin SSD-40IR BID
- Treatment B:Placebo BID

3.3 Procedures for Breaking the Blind

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of the participant, will the investigator be allowed to unblind a participant's treatment assignment. To discuss breaking of the blind, the investigator should contact the Medical Monitor. The investigator will unblind via an Interactive Response Technology system.

If the investigator breaks the blind for an individual participant, the reason must be in the participant's source documents and the participant will be removed from the study.

4.0 SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Inclusion Criteria

A participant will be eligible for inclusion in this study if he/she meets all of the following criteria:

1. Participant has a diagnosis of advanced liver cirrhosis with medically controlled ascites (> 30 days) not requiring therapeutic paracentesis (prophylactic variceal banding allowed if no history of previous variceal bleeding).

   Cirrhosis diagnosis can be made using any of the following:

   - Histopathological evidence of cirrhosis
   - Magnetic resonance imaging (MRI)
   - Computed tomography (CT)
   - Fibroscan (Transient Elastography)
   - Imaging (sonographic or cross-sectional)
   - Presence of esophageal varices
   - Thrombocytopenia (< 150,000/μL) in participants with CLD
2. Participant has a Child-Pugh B Classification (score of 7 to 9 inclusive) without OHE.
3. Participant has a Conn (West Haven Criteria [WHC]) score of < 2.
4. Participant has a Mini-Mental State Examination (MMSE) score ≥ 24 at screening and baseline.
5. Participant is ≥ 18 and ≤ 85 years of age.
6. Females of childbearing (reproductive) potential must have a negative serum or urine pregnancy test at screening. All participants must agree to use 2 acceptable methods of contraception throughout their participation in the study (see Section 7.11).
7. Participant must be able to independently read, fully understand and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form (ICF) without additional support and provide authorization as appropriate per local privacy regulations.

4.2 Exclusion Criteria

A participant will not be eligible for inclusion in this study if any of the following criteria apply:

1. Participant has an active COVID-19 infection that is unresolved or, in the opinion of the investigator, may affect evaluation of the study drug or might place the subject at undue risk.
2. Participant has a history of anaphylaxis or hypersensitivity to rifaximin, rifampin, rifamycin antimicrobial agents, or any of the components of rifaximin.
3. Participant has a history of SBP, primary or secondary SBP prophylaxis, EVB, or AKI-HRS.

- AKI-HRS diagnostic criteria: ≥ Stage 2 AKI; no improvement of serum creatinine after ≥ 48 hours of diuretic withdrawal and volume expansion with albumin at a dose of 1 g/kg of body weight, up to a maximum of 100 g daily; absence of hypovolemic shock or infection that require vasoactive drugs to support blood pressure; no current or recent use of nephrotoxic drugs; proteinuria < 500 mg/day, and hematuria <50 RBC/high power field.

4.

   a. Participant has a documented history of an OHE episode (Conn score ≥ 2).

   b. Participant has a history of rifaximin 550 mg and lactulose use for suspected OHE episode. Short course (≤ 2 weeks) of rifaximin for non-OHE indications (e.g., Traveler's Diarrhea or Irritable Bowel Syndrome with Diarrhea indications), > 90 days prior to screening is allowed. Occasional and intermittent use of lactulose (≤ 2 weeks) for non-OHE indications (e.g., constipation or for testing purposes, like lactulose breath test), > 1 weeks prior to screening is allowed.

5. Participant has other uncontrolled neurological or psychiatric conditions which may confound the assessment of cognitive function (e.g., dementia, schizophrenia, etc.). Participants with generalized seizure within 30 days prior to screening are excluded.
6. Participants with focal neurological deficits due to a neurological event such as cerebrovascular accident.
7. Participants with Wernicke's or Wernicke-Korsakoff encephalopathy.
8. Participant has pseudomembranous colitis, abdominal abscess, or clinically significant strictures and fistulas of the gastrointestinal tract.
9. Participant consumes more than moderate amounts of alcohol, defined as 1 standard drink per day for women and 2 standard drinks per day for men.
10. Participant has a history of substance abuse < 6 months prior to signing the ICF and cannot refrain from substance abuse during the study period. For alcohol abuse, participants undergoing alcohol use counseling or receiving Alcohol Use Disorder pharmacotherapy, can be considered for inclusion.
11. Participants on antipsychotic medications should be excluded irrespective of indication or dose. Benzodiazepine, psychoactive medicine, and opioid use are excluded, with the exception of:

    a. Participants on psychoactive medications with a washout period of 30 days before providing consent. Participants on stable and low-dose psychoactive medicines, may be included, as well as participants on stable low dose of short-acting

benzodiazepines, taken at night and not for more than 3 nights per week, for the last 2 weeks.

b. Participants are allowed on a stable opioid dose, where the total chronic and breakthrough (pro re nata [PRN]) doses do not exceed 100 milligrams morphine equivalents (MME), for at least 2 weeks, with 3 or more satisfactory bowel movements per week in the last 2 weeks without the aid of laxatives or on stable dose of laxatives.

12. Participant is currently taking Warfarin that cannot be discontinued. If there is a washout period of 7 days or more before informed consent for participants taking Warfarin, they may be included.
13. Participant has been diagnosed with an uncontrolled infection < 4 weeks prior to screening.
14. Participant has been diagnosed with an upper gastrointestinal bleed from non-variceal sources < 6 weeks prior to screening.
15. Participant shows presence of intestinal obstruction or has inflammatory bowel disease.
16. Participant has undergone bariatric surgery or intestinal resection. Limited segmental resection of colon (e.g., adenomatous polyp) > 2 years prior is allowed.
17. Participant has a history of portal vein thrombosis, a history of a TIPS procedure, or plans to undergo a TIPS procedure.
18. Participant has a history of shunt surgery or direct intrahepatic portocaval shunt (DIPS) procedure for portal hypertension or plans to undergo a DIPS procedure.
19. Participant requires peritoneal dialysis or hemodialysis.
20. Participant has undergone prophylactic variceal banding within 2 weeks of screening or is scheduled to undergo prophylactic variceal banding during the study (Note: participants with previous prophylactic variceal banding will be allowed to participate in the study).
21. Participant has Type 1 or Type 2 diabetes that is not adequately controlled in the opinion of the investigator.
22. Participant has severe co-morbid disease with a life expectancy < 1 year.
23. Participant has active malignancy (except basal carcinoma of the skin), including active hepatocellular carcinoma (HCC) and/or a past history of HCC. Participants with resections or ablations of squamous cell carcinoma of the skin, or in situ carcinoma of the cervix, that occurred greater than 6 months prior to screening and are considered disease free are eligible for enrollment.
24. Evidence of HCC or a lesion suspicious for HCC <u>within 6 months</u> on ultrasound or contrast multiphase MRI or CT. If this imaging is not available, or if alpha-fetoprotein (AFP)

≥ 20 ng/ml at screening, participants should undergo standard of care diagnostic procedures with their personal physician to rule out HCC during the screening period.

25. Participant has any condition or circumstance that adversely affects the participant, could cause noncompliance with treatment or visits, may impact the interpretation of clinical data, could cause bias, or may otherwise contraindicate the participant's participation in the study.
26. Participant used any investigational product or device within 30 days or 5 half-lives of the investigational product (whichever comes first) of providing consent.

4.3 Concomitant Therapies

All prior medications administered within 30 days of Visit 1 (screening) and all concomitant medications (CMs) will be recorded in the participant's medical record and on the CM page of the electronic case report form (eCRF).

4.3.1 Permitted Therapy

The following therapies are permitted during the study.

- Stable dose of antidepressants which are expected to remain unchanged throughout the trial.
- Over the counter laxatives or stool softeners will be allowed to treat constipation at the discretion of the investigator but should be used sparingly to avoid diarrhea.
- A short-course of antibiotic therapy (≤ 10 days; non-rifamycin and non-quinolone classes only) to treat non-cirrhosis-related conditions such as sinusitis, dental therapy prophylaxis, urinary tract infections, etc. Longer courses of therapy will require the permission of the sponsor.
- P-glycoprotein (P-gp) inhibitor treatment is permitted as long as the use of P-gp inhibitors is discussed with the investigator. Additional considerations regarding P-gp inhibitor use are described in Section 6.3. P-gp inhibitors include, but are not limited to cyclosporine A, non-selective beta blockers (excluding nadolol), HIV protease inhibitors, azole antifungals, macrolide antibiotics, non-dihydropyridine calcium channel blockers. NOTE: This is NOT A COMPLETE LIST.

4.3.2 Prohibited Therapy

If a participant experiences an AE and/or an OHE episode, the investigator should treat according to standard of care. Any prohibited medications used during the study will be recorded on the CM page of the eCRF.

The following CM are prohibited as specified:

- Non-study rifaximin (e.g., commercial rifaximin, Xifaxan® 550 mg tablets), rifampin or other rifamycin derivatives are prohibited within 90 days of providing consent, and throughout the study.
- Use of Warfarin within 7 days of providing informed consent and throughout the study.
- Lactulose/lactitol, neomycin, metronidazole, pre/probiotic capsules, L-ornithine-L-aspartate, or branched chain amino acids within 30 days of providing consent, and throughout the study. Occasional and intermittent use of lactulose (≤ 2 weeks) for non-OHE indications (e.g., constipation or for testing purposes, like lactulose breath test), > 1 weeks prior to screening is allowed. Fecal or intestinal microbiota transplantation during the study and within 1 year of providing consent, are prohibited.
- Participants on antipsychotic medications should be excluded irrespective of indication or dose. Benzodiazepine, psychoactive medicine, and opioid use are excluded, with the exception of:
    - Participants on psychoactive medications with a washout period of 30 days before providing consent. Participants on stable and low-dose psychoactive medicines, may be included, as well as participants on stable low dose of short-acting benzodiazepines, taken at night and not for more than 3 nights per week, for the last 2 weeks.
    - Participants are allowed on a stable opioid dose, where the total chronic and breakthrough (PRN) doses do not exceed 100 MME, for at least 2 weeks, with 3 or more satisfactory bowel movements per week in the last 2 weeks without the aid of laxatives or on stable dose of laxatives.
- Chronic antibiotic use throughout the study is prohibited. A short-course of antibiotic therapy (≤ 10 days; non-rifamycin and non-quinolone classes only) to treat non-cirrhosis-related conditions such as sinusitis, dental therapy prophylaxis, urinary tract infections, etc. is permitted. Longer courses of therapy will require the permission of the sponsor.
- Investigational drug use within 30 days of providing consent, and throughout the study.
- Gabapentin and pregabalin are prohibited because they may potentially affect assessment of mental status and diagnosis of OHE, even when they are administered at a stable dose for a long time.

If prohibited medication use is discovered and the prohibited medication has already been discontinued, or can be safely discontinued per the investigator's judgment, the participant may continue study medication at the investigator and sponsor's discretion. Otherwise, the participant should discontinue study treatment and be followed until the end of the 72-week trial.

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. Indeed, initiation of OHE therapy is one of the factors considered when determining whether an OHE event (the primary endpoint of the study) has occurred.

If a participant prematurely discontinues study treatment, every attempt will be made to obtain EOT and EOS assessments and the participant should be followed until the end of the 72-week trial.

4.4 Females of Reproductive Potential

There are no adequate and well controlled studies in pregnant women. Rifaximin has been shown to be teratogenic in rats and rabbits at doses that caused maternal toxicity.

Female study participants of childbearing (reproductive) potential must have a negative serum or urine pregnancy test at Visit 1 (screening) and a negative serum or urine test result at the Randomization Visit (Visit 2) must be documented prior to the first study drug administration. Female study participants of childbearing (reproductive) potential agree to use an acceptable method of contraception throughout their participation in the study (see details in Section 7.11). If a female participant becomes pregnant while on this study, the study drug will be immediately discontinued, and the participant will be followed until the outcome of the pregnancy is known. The pregnancy will be reported to Salix using the guidelines provided in Section 7.9 and Section 7.10.

4.5 Premature Participant Discontinuation

A participant may be discontinued from treatment and/or the study for any of the following reasons:

Study treatment should be discontinued if:

- Participant develops OHE
- Participant has a liver transplant during the study
- 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) increases ≥ 1 over the baseline
- Subject meets the criteria for acute-on-chronic liver failure (ACLF; Appendix 4).

- Occurrence of an AE and/or SAE that suggests an unacceptable risk to the participant, in the judgment of the investigator, including worsening of the disease under study.
- Pregnancy (see Section 7.9 for further details).

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:

- Participant request to withdraw
- Investigator discretion
- Sponsor decision to terminate the study
- A subject with an active COVID-19 infection that, in the opinion of the investigator, may affect evaluation of the study drug or might place the subject at undue risk

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

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. Participants who terminate early for reasons other than death will be contacted approximately 72 weeks from randomization to determine if they experienced an event of OHE and if so, when that event occurred; for participants who did not experience an OHE event, data will be censored at the time of last contact. Whether a participant attends a visit or is contacted by telephone, once a possible event that may require adjudication is noted, medical records must be obtained and submitted to the CEAC for adjudication of the event.

For all cases of premature discontinuation from the study, regardless of the cause, the investigator must provide the reason for discontinuation on the appropriate eCRF. Participants should be followed for 28 days after last administration of study drug, and every attempt should be made to obtain EOT and EOS assessments.

If a participant prematurely discontinues treatment with investigational drug at any time due to an AE or SAE, every attempt will be made to obtain EOT and EOS assessments and the participant should be followed until the end of the 72-week trial, or for 28 days, or until resolution or stabilization of the condition resulting in withdrawal has been confirmed, whichever comes later.

4.6 Study Contact Information

The investigator may deem it necessary to perform special tests, to hospitalize the participant, or to prescribe CMs. The study manager should be first point of contact for any questions related to the study.

5.0 TREATMENT OF PARTICIPANTS

5.1 Formulation and Supply

Description of Active Treatment

Rifaximin SSD-40IR will be supplied as light blue-colored, coated, round, biconvex tablets containing 40 mg of rifaximin. Inactive ingredients include: hypromellose acetate succinate, poloxamer 407, croscarmellose sodium (CCS), microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and FD&C Blue #2. The concentration of the intragranular excipient CCS controls the drug release rate. IR tablets contain 10% w/w CCS.

Description of Comparator Treatment

Placebo will be supplied as tablets that look like the rifaximin SSD tablets but only containing inactive ingredients. The components used in the manufacture of the placebo are hypromellose acetate succinate, poloxamer 407, croscarmellose sodium, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Blue #2.

5.2 Packaging and Labeling

The rifaximin SSD-40IR tablets and SSD placebo tablets will be packaged and labeled in a manner consistent with the study design and according to applicable national/regional and local regulations for an investigational drug.

5.3 Storage and Handling

All study drug will be kept in a locked area with limited access. All bottles of study drug must be stored at 20º-25º C (68º-77º F) with excursions permitted to 15º-30º C (59º-86º F). Study drug will be dispensed by qualified study staff only in accordance with the procedures described in this protocol.

5.4 Dosing and Dosing Schedule

Each participant will be dispensed study drug according to the schedule in Appendix 1, Time and Events Schedule, in an adequate amount to allow proper dosing to the next scheduled study visit.

During the Treatment Period, eligible participants will take 1 tablet of study drug BID according to their treatment assignment as explained in Section 3.2. Dosing will begin on Study Day 1 (Visit 2). Doses will be taken orally with water, and tablets will be swallowed whole.

Before any study drug is administered, each participant will be instructed by the investigator or his/her representative on the proper self-administration of study drug. All unused study drug will be returned to the study center at the next clinic visit.

5.5 Rationale for Dose Selection

The dose and formulation of rifaximin SSD proposed for the Phase 3 study are based on the safety and efficacy of rifaximin SSD-40IR in two Phase 2 clinical studies and the PK of this formulation. Study RNLC2131 evaluated the prevention of hospitalization for complications of liver cirrhosis or all-cause mortality in participants with early decompensation and Study RNHE2041 evaluated the efficacy and safety of rifaximin SSD tablets plus lactulose in participants hospitalized with OHE. As described in Section 1.3, rifaximin SSD-40IR showed efficacy in reduction of risk preventing HE-related complications of liver cirrhosis and significantly decreasing the time to OHE resolution.

5.6 Study Drug Accountability

All study drug will be kept in a secure, temperature-controlled area with limited access. Investigational drug orders, records of study drug receipt, dispensing, and running inventory will be examined and reconciled throughout the study. Upon the completion of the study, this material will be subjected to final inspection and reconciliation. Instructions will be provided by the sponsor regarding final disposition of all study medication in compliance with applicable regulations.

Study drug reconciliation will be conducted during monitoring visits to ensure appropriate receipt, storage, dispensing, and documentation of returned study drug.

5.7 Assessment of Compliance

After study drug is dispensed, the investigator or his/her representative will count and record the unused study drug tablets that are returned by the participant at each visit. If the participant forgets to return unused study drug at a visit, then compliance will be confirmed after direct questioning of the participant. The investigator's judgment of compliance will be accepted.

6.0 STUDY PROCEDURES AND ASSESSMENTS

A schedule of assessments to be performed during the study is provided in Appendix 1, Time and Events Schedule. For this study, Day 1 (Visit 2), which is the day of randomization, shall be defined as the participant’s baseline.

In case of pandemic or other situations that prevent a participant from attending a post-baseline study visit, a home health visit may be scheduled, where possible. The home health visit may include an assessment of changes in health and medications, measurement of vital signs and body weight, safety laboratory blood and urine sample collection, collection of blood samples for PK analysis (if applicable), and checking of study medication compliance. The home health professional may also encourage the participant to complete any applicable study questionnaires via the backup website. All documented assessments and laboratory results will be reviewed by the investigator and documented in relevant eCRFs as appropriate.

6.1 Study Schedule by Treatment Visit

6.1.1 Visit 1; Screening (Day –28 to Day –1)

The initial Screening Visit (Visit 1) should be conducted between Days -28 and -1, inclusive. The following procedures are to be completed at Visit 1:

1. Informed consent signed by the participant prior to performing any study evaluations or procedures including asking participants to discontinue any prohibited medications
2. Demographics and Medical History information should be recorded. First diagnosis of liver cirrhosis should be documented
3. Inclusion/Exclusion criteria review to ensure participant qualifies for the study
4. Subject[1] identification number should be assigned
5. Obtain vital signs
6. Electrocardiogram (ECG; 12-lead)
7. Full physical examination including height and weight
8. Serum or urine pregnancy test for females of childbearing potential
9. Hematology, blood chemistry, coagulation (prothrombin time [PT]/INR), ethyl glucuronide (EtG), and urinalysis
10. Alpha-fetoprotein
11. Conn (WHC) score
12. MELD score and MELD-Na score
13. Child-Pugh score and classification
14. MMSE
15. CMs (record all within 30 days of Visit 1)
16. Participants should discontinue use of prohibited medications immediately after Visit 1 (screening)
17. AEs
18. Schedule Visit 2

[1] The terms “subject” and “participant” where applicable are interchangeable

6.1.2 Visit 2; Randomization (Day 1)

The Randomization Visit will be performed on Day 1. There is no Day 0 in this protocol. The following assessments are to be completed prior to randomization:

1. Inclusion/Exclusion Review to ensure participant continues to qualify for the study
2. Short Form-36
3. ANT
4. Vital sign measurements and weight
5. Symptom-directed physical exam, as needed
6. Serum or urine pregnancy test for females of childbearing potential
7. Hematology, blood chemistry, coagulation (PT/INR), EtG, and urinalysis
8. Conn score
9. MELD score and MELD-Na score
10. Child-Pugh score and classification
11. MMSE
12. Randomization/Treatment number assignment
13. Caregiver Reported Burden
14. Dispense study drug (4-week supply)
15. CMs
16. AEs
17. Instruct participant to take study drug BID
18. For participants in the PK substudy only: collect pre-dose PK blood sample
19. Administer first dose
20. For participants in the PK substudy only: collect PK blood samples at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dose; the 12-hour PK draw must be performed before administration of the next scheduled dose
21. Schedule Visit 3

6.1.3 Visits 3 Through 12; Week 4 Through Week 68

The following assessments are to be completed at Visits 3 through 12:

1. Record time and date of the 2 most recent study drug doses taken prior to visits

2. Collect and record hospital admission or death data
3. Short Form-36
4. ANT (Visits 4, 6, 8, and 10)
5. Vital sign measurements and weight
6. Symptom-directed physical exam, as needed
7. Serum or urine pregnancy test for females of childbearing potential
8. Hematology, blood chemistry, coagulation (PT/INR), EtG and urinalysis
9. Visit 3, Visit 8, and Visit 12 (or Last Study Visit for participant dropouts) only, all participants: collect a pre-dose blood sample for PK analysis
    - **For PK substudy participants only, Visit 3:** collect PK blood samples at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dose; the 12-hour PK draw must be performed before administration of the next scheduled dose
10. Conn score
11. MELD score and MELD-Na score
12. Child-Pugh score and classification
13. Caregiver Reported Burden since last visit
14. Collect unused study drug
15. Assess dosing compliance
16. Dispense study drug according to the following schedule:
    - At Visit 3, dispense a 4-week supply
    - At Visit 4, dispense a 4-week supply
    - At Visit 5, dispense a 8-week supply
    - At Visit 6, dispense a 8-week supply
    - At Visit 7, dispense a 8-week supply
    - At Visit 8, dispense a 8-week supply
    - At Visit 9, dispense a 8-week supply
    - At Visit 10, dispense a 8-week supply
    - At Visit 11, dispense a 8-week supply
    - At Visit 12, dispense a 4-week supply

17. Record CMs
18. Record AEs
19. Review dosing instructions
20. Schedule the next Visit.

- At Visit 5 (Week 12), remind participant of Week 16 Telephone Call ([TC]1)
- At Visit 6 (Week 20), remind participant of Week 24 Telephone Call (TC2)
- At Visit 7 (Week 28), remind participant of Week 32 Telephone Call (TC3)
- At Visit 8 (Week 36), remind participant of Week 40 Telephone Call (TC4)
- At Visit 9 (Week 44), remind participant of Week 48 Telephone Call (TC5)
- At Visit 10 (Week 52), remind participant of Week 56 Telephone Call (TC6)
- At Visit 11 (Week 60), remind participant of Week 64 Telephone Call (TC7)

6.1.4 Telephone Calls 1 to 7, (Weeks 16, 24, 32, 40, 48, 56, and 64)

1. Record time and date of 2 last study drug doses
2. Assess dosing compliance
3. Assess if an unscheduled visit is warranted, if hospital admissions have occurred, and whether or not there have been any new, or changes to, AEs and CMs
4. Review dosing instructions

6.1.5 Visit 13, Week 72 (Day 504 ± 3 days)/EOT Visit

The following assessments are to be completed at the EOT Visit:

1. Record time and date of last study drug dose
2. Collect and record hospital admission data
3. Short Form-36
4. ANT
5. Vital sign measurements and weight
6. Full physical exam
7. Serum or urine pregnancy test for females of childbearing potential
8. Hematology, blood chemistry, coagulation (PT/INR), EtG, and urinalysis
9. Conn score

10. MELD score and MELD-Na score
11. Child-Pugh score and classification
12. Caregiver Reported Burden since last visit
13. Collect unused study drug
14. Assess dosing compliance
15. CMs
16. AEs

6.1.6 Visit 14, Week 76/EOS Visit (28 ± 3 Days Following the EOT Visit)

The following assessments are to be completed at the EOS Visit:

1. Collect and record hospital admission data.
2. Vital sign measurements and weight.
3. Symptom-directed physical exam.
4. Serum or urine pregnancy test for females of childbearing potential.
5. Hematology, blood chemistry, coagulation (PT/INR), EtG, and urinalysis as appropriate for following/resolution of AEs.
6. Conn score.
7. MELD score and MELD-Na score.
8. CMs.
9. AEs.

6.1.7 Unscheduled Visit

The investigator may perform an unscheduled visit at any time during the study at his/her discretion. Assessments performed at an unscheduled visit should be symptom-directed; if the reason for an unscheduled visit is to perform a PK sample, then a PK sample should be taken.

The following procedures must be performed at all unscheduled visits:

1. Collect and record hospital admission and death data
2. Conn score
3. MELD score and MELD-Na score
4. Child-Pugh score and classification

5. Blood sample for PK, if applicable
6. Safety laboratory testing, including EtG. Repeat laboratory testing may be needed based on results from the unscheduled laboratory testing
7. CMs
8. AEs
9. Caregiver Reported Burden

If the participant is discontinued from the study at an unscheduled visit, the visit will be considered Visit 13 (EOT) and all of the EOT assessments should be completed. When possible, the participant should return 4 weeks later for Visit 14 (EOS). If a participant prematurely discontinues treatment, every attempt will be made to obtain EOT and EOS assessments and the participant should be followed until the end of the 72-week trial.

6.2 Assessment of Efficacy

Efficacy endpoints are presented in Section 2.2.1. Analyses of efficacy endpoints are described in Sections 8.4.1 and 8.4.2.

The following assessments will be utilized throughout the study.

6.2.1 Adjudication of Suspected OHE Endpoints Clinical Event Adjudication Committee

Suspected OHE events in the study will be centrally adjudicated by an independent clinical events committee. Suspected OHE events in the study will be identified either by the investigator or by electronic review of reported AEs. For all events identified for adjudication the investigator will complete the appropriate modules of the eCRF and provide source documentation. Guidance for "reporting potential clinical endpoints" is provided in the Event Reporting Manual. Definitions of OHE events, the makeup of the CEAC, and the process for event adjudication are detailed in the CEAC Charter.

6.2.2 Conn Score

The Conn score (also known as the WHC) is a 5-point scale (0 to 4) for grading the severity of HE based upon neurocognitive function (Conn, 1977). Clinically, people with a Conn score of 2 or higher are diagnosed as having OHE. The Conn scale is criticized for its subjectivity, and extreme intra- and inter-observer variability, particularly in identifying patients in Grade I category. The reliable presence of OHE can be minimized by using 'disorientation to time' and 'asterixis' as criteria for Grade II HE which also leads to good inter-rater and inter-site reliability of the Conn in identifying patients in Grade II (see Appendix 6).

6.2.3 Model End-Stage Liver Disease

MELD is a scoring system used in assessing the severity of CLD.

MELD score will be calculated at 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 at the central laboratory using the following formula:

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

6.2.4 36-Item Short Form Health Survey

The SF-36 (Appendix 2) is a validated, widely used questionnaire designed to measure functional health and well-being from the participant's point of view. It uses 36 questions to assess 8 health concepts: 1) limitation in physical activities because of health problems, 2) limitations in social activities because of physical and emotional problems, 3) limitations in usual role activities because of physical health problems, 4) bodily pain, 5) general mental health, 6) limitations in usual role activities because of emotional problems, 7) vitality, and 8) general health perceptions. It will be used to measure HRQL changes during and in response to treatment.

6.2.5 Zarit Caregiver Reported Burden

The Zarit Burden Inventory (Appendix 3) contains 22 questions and can be considered as a cumulative risk measure. Higher scores indicate that caregiving has greater impact on the caregiver's life. All items are scored on a 5-point scale ranging from 0 to 4. The Zarit Burden Inventory can be used in research to track changes over time and as a measure of treatment outcomes.

6.2.6 Hospital Admissions and Emergency Room/Emergency Department Visits

Hospital admission data for all SAEs requiring hospitalization or emergency department (ED) visits will be captured. The source documents and eCRF, as applicable, for all hospitalizations should include the information as described below for suspected OHE episodes.

Participants and caregivers should be instructed to go to their local emergency department (or an ED pre-determined with the investigator) with any suspected episode of OHE to appropriately document the event per the protocol. In the event a randomized participant is admitted to the hospital for complications of liver cirrhosis (HE, EVB, SBP, renal failure in the presence of ascites, or ascites requiring paracentesis), it is important that the following information be captured in the source documents (and eCRF, as applicable):

- The date of the hospital admission.
- The associated liver cirrhosis complication leading to the hospital admission.

- The first day that the participant begins experiencing symptoms of liver cirrhosis complications.
- Treatment received in the hospital.
- The date of discharge, discharge summary, all available hospital records including laboratory results, test results, history and physical, procedures performed, and consults.

The investigator must make every effort to determine when the onset of symptoms for liver cirrhosis complications first developed, which may include, for example, a retrospective review of medical records from a treating physician and/or a discussion with the caregiver or participant regarding the symptoms experienced. The Conn score will be confirmed by the investigator based on the documentation from a qualified medical professional at the hospital and recorded on the eCRF page.

The investigator must make every effort to determine whether the episode resulted from a precipitating event (e.g., GI bleeding) or arose from unknown causes, which will be documented in the participant's source documents and eCRF.

ED visits will be adjudicated to judge whether the visit and treatment received meet the criteria to be included in the analysis of the primary endpoint.

6.3 Assessment of Pharmacokinetics

For all participants, pre-dose blood samples for analysis of plasma rifaximin and 25-desacetyl rifaximin PK will be collected during the following visits:

- Visit 3 on Week 4
- Visit 8 on Week 36
- Visit 12 on Week 68 [or the Last Study Visit in case of a participant dropout]

For participants in the PK substudy (n = 10 per treatment arm; 20 subjects total), blood samples for noncompartmental analysis of plasma rifaximin will be collected at the following timepoints:

- Visit 2 (Day 1) and Visit 3 (Week 4): pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dose

The date and time of the last 2 rifaximin doses prior to the clinical visit will be recorded.

If the participant is to begin treatment with a P-gp inhibitor, a plasma sample for PK analysis should be collected during treatment with both rifaximin and the P-gp inhibitor and Medical Monitor made aware. This sample should be collected at the next scheduled visit, unless the P-gp Inhibitor will be discontinued prior to the next visit. If the P-gp Inhibitor will be discontinued prior to the next scheduled visit, an unscheduled PK sampling visit should occur prior to discontinuation of the P-gp inhibitor. At the time of PK sampling, the date and time of the last 2 rifaximin doses, as well as the last 2 doses of the P-gp inhibitor should be recorded.

If any participant has an SAE, a plasma sample for PK analysis should be collected as soon as feasible. The time of the 2 last doses of rifaximin should be recorded.

6.4 Assessment of Safety

Safety endpoints are presented in Section 2.2.2. Safety assessments will include the following:

- Incidence of TEAEs, SAEs, and infections
- Clinically significant changes from baseline in clinical laboratory results
- Changes from baseline in vital sign measurements
- All-cause mortality

6.4.1 Clinical Laboratory Tests

The following clinical laboratory tests are to be performed during the study and will be analyzed by a central clinical laboratory. At the investigator's discretion, additional blood may be collected for clinical laboratory tests. Results from laboratory specimens collected during screening must be received by the site prior to Visit 2.

Hematology, Chemistry, Coagulation, Ethyl Glucuronide, and Urinalysis

Clinical laboratory tests performed during the study will be analyzed by a central clinical laboratory.

- Hematology: Complete Blood Count 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
- In the event of a suspected infection, investigators may have culture and sensitivities performed at a local laboratory
- Coagulation: PT and INR
- EtG: Urine
- Urinalysis: Routine urinalysis with microscopic examination if a urinary tract infection is suspected

6.4.2 Pregnancy Tests

At each visit a pregnancy test will be performed for all females of childbearing potential. The serum or urine pregnancy test must be confirmed as negative at each visit before the dispensing/administration of study drug.

6.4.3 Adverse Events

The investigator is responsible for the detection and documentation of events that meet the definition of an AE or SAE as provided in this protocol. Assessments of occurrences of AEs or SAEs should be conducted during each study visit or as reported by the participant outside of scheduled visits. In order to fulfill safety reporting obligations, the investigator should include in his or her assessment any AEs resulting from study participation regardless of relation to study drug (e.g., complications resulting from the taking of a blood sample).

6.4.4 Vital Signs

Vital signs will include blood pressure (mmHg), heart rate (beats per minute), respiratory rate, weight, and temperature. Vital sign measurements will be collected at every visit. Participants should be seated for 5 minutes prior to assessment of vital signs. Blood pressure measurements should be measured on the same arm throughout the study. Weight will be collected every visit, but height will only be collected at Visit 1 (screening).

6.4.5 Electrocardiogram

A 12-lead ECG (at rest) will be performed on all participants using a standard ECG machine. The investigator will evaluate if the participant should enter the study based on any findings on ECG.

6.4.6 Physical Examination

A physical examination will be performed at Visit 1 (screening) and Visit 13 (EOT). Symptom-directed physical examinations will be performed at Visits 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 14 (EOS) as needed.

6.5 Other Assessments

6.5.1 Medical History

Each participant's complete medical history is to be recorded in source documents and the appropriate eCRF pages. Relevant medical history (including past enteric infections) will include a detailed history of the participant's liver cirrhosis and affiliated liver cirrhosis complications (e.g., date and onset, surgical history, location, etc.).

6.5.2 Mini-Mental State Examination

The MMSE is a brief screening test that quantitatively assesses the severity of cognitive impairment and documents cognitive changes occurring over time. It includes 11 questions that test cognitive function, orientation, attention, memory (immediate and short-term recall), language, and the ability to follow simple verbal and written commands. It will be used to assess and confirm eligibility to participate in this study.

6.5.3 Child-Pugh Classification

The Child-Pugh classification system for the severity of liver disease is shown in Appendix 5. The classification system determines severity of liver disease according to the degree of ascites (via clinical assessment), the serum concentrations of bilirubin and albumin, INR, and the degree of encephalopathy. It will be used to assess eligibility to participate in this study and to monitor the participant's liver disease throughout the treatment phase.

6.5.4 Animal Naming Test

Subclinical HE may be difficult to detect. The 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. Appendix 7 outlines the instructions for administering the test.

7.0 SAFETY REPORTING

7.1 Operating Definitions for Assessing Safety

Safety data collection for this study begins at the time of the participant's signing of the informed consent according to the operating definitions defined in this section of the protocol. The investigator is responsible for the detection and documentation of events that meet the definition of an AE (Section 7.1.1), or SAE (Section 7.1.2).

7.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical investigation participant 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 AEs, but primary efficacy endpoint.
- 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 participant's usual clinical course; unless the participant experiences worsening of their symptom(s) or the symptom(s) meet the criteria for an SAE (exception is OHE and presenting symptoms).

7.1.2 Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was, in the view of the investigator or sponsor, at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered to be an AE. "Inpatient" hospitalization means the participant has been formally admitted to a hospital for medical reasons for 24 hours or more. It does not include presentation at a casualty or emergency room.

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect in the offspring of a participant 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 participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in case of events that do not meet the serious criteria.

If a participant has an SAE, a plasma sample for PK analysis will be collected as soon as feasible, and the date and time of the last 2 rifaximin doses will be recorded.

7.1.3 Adverse Events of Special Interest

Long-term use of antibiotics with a broad-spectrum of action and high systemic absorption increases the risk of developing drug-resistant organisms. The minimal systemic absorption of rifaximin SSD-40IR reduces the likelihood of the development of resistance, but the long course of treatment in this study increases the risk. In previous clinical trials in subjects with cirrhosis and in clinical practice with the currently marketed formulation of rifaximin, there have been rare reports of rifampin-resistant *Clostridium difficile* infections.

Because of the potential for development of antibiotic-resistant bacteria, particularly enteric organisms, and because patients with cirrhosis have an increased risk of bacterial infections that can trigger liver decompensation, bacterial infections will be closely monitored as adverse events of special interest (AESIs). To perform this enhanced surveillance, investigators must report suspected or confirmed bacterial infections as AEs or SAEs to the sponsor within 24 hours of awareness, using the AESI/SAE report form. Investigators should conduct appropriate testing to identify the causative organism and antibiotic susceptibility (particularly to rifampin), and submit these results in follow-up reports.

7.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, coagulation) or other abnormal assessments (e.g., abnormal findings during examinations, the taking of vital signs, or ECG monitoring) that are judged by the investigator as clinically significant must be recorded as AEs or SAEs if they meet the definition of an AE or SAE. The investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment (including ECG monitoring) is clinically significant. Abnormal laboratory findings consistent with pre-existing illness or confirmatory of a reported AE or SAE should not be reported as a separate AE or SAE. If a clinically significant change from baseline is observed which is indictive of worsening in condition, then the worsening condition should be reported as the AE or SAE.

7.3 Method, Frequency, and Time Period for Detecting AEs and SAEs

At each assessment, after the participant (or caregiver) has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the following questions:

1. Have there been any (other) medical problems since your last visit/assessment?"
2. Have any new medications been taken, other than those given to you in this study, since your last visit/assessment?"

7.3.1 Time Period for Detecting and Reporting of AEs and SAEs

From the time of informed consent through study completion/withdrawal, including the Follow-up Period.

7.3.2 Post-Study SAEs

Investigators are not obligated to actively seek SAE information in former study participants, but investigators are encouraged to notify the sponsor/designee of any SAEs occurring at any time after a participant has discontinued or terminated study participation that they judge may reasonably be related to study treatment or study participation.

7.4 Documenting AEs and SAEs

All AEs that occur after the participant has signed the ICF through 28 days after last dose of study medication, regardless of causality or seriousness, will be assessed and recorded in the participant's source documents and in the eCRF. In addition, AESIs and SAEs must be documented on the paper AESI/SAE Report Form.

The investigator should attempt to establish a diagnosis for the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE or SAE and not the individual signs/symptoms. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the participant at each study visit. Each AE which appears to be independent of any prior event will be reported separately.

For clinically significant abnormal laboratory findings or other abnormal assessments meeting the definition of an AE or SAE, a diagnosis, if known (or clinical signs and symptoms if a diagnosis is unknown), should be recorded by the investigator. If a diagnosis is unknown and clinical signs and symptoms are not present, then the abnormal finding should be recorded. When documenting an AESI or SAE on the AESI/SAE Report Form, relevant laboratory (including the reference range and units) or copies of the laboratory report (with reference ranges and units) should be sent with the SAE Report Form.

The AESI/SAE Report Form should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to the sponsor/designee. Investigators should not wait to receive additional information to fully document the event before notifying the Sponsor of an AESI/SAE. It is very important that the investigator (or designee) provide his/her assessment of causality to study product at the time of initial AESI/SAE reporting.

7.5 Common Terminology Criteria for Adverse Events

The severity of events will be determined based on CTCAE, version 5.0. The CTCAE quick reference guide can be found at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

For events not specifically addressed in the CTCAE, the following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal local or noninvasive intervention indicated limiting age-appropriate instrumental Activities of Daily Living (ADL)*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE
ADL * Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. ** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

7.6 Assessment of Causality

The investigator should assess the relationship of the AE, if any, to the study drug as either "Related" or "Not Related." The following should be taken into account when assessing AE causality:

- Related: There is at least a reasonable possibility that the AE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
- Not Related: There is little or no reasonable possibility that the AE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

The following should be taken into account when assessing AE causality:

- Positive temporal relationship to study drug, such as if study drug was withdrawn and the SAE resolved, or the event recurred after re-introduction.
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness.
- Possible association with previous or concomitant therapy.
- No temporal relationship to treatment with study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures.

7.7 Follow-up of AEs, AESIs, and SAEs

All AEs, regardless of seriousness, must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, relevant hospital records (i.e. discharge summary), or consultation with other health care professionals.

Salix may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a participant dies during participation in the study or during the Follow-up Period, the sponsor/designee should be provided with a copy of any postmortem findings, including histopathology.

If cause of death is not available within the 24-hour reporting period, “death” must be reported as SAE term to meet timelines and the cause of death actively queried and submitted as a follow-up report.

When additional AESI/SAE information becomes available, it should be recorded on a new report form and should be labeled as a “follow-up report”. The original SAE Report Form should not be altered. All completed AESI/SAE Report Forms must be signed and dated by the investigator or designee. By signing the form, the investigator or designee attests to the accuracy and completeness of the data and that he/she has reviewed and approved the report being submitted.

The investigational sites IRB/EC must be notified in accordance with the requirements of the governing IRB/EC.

7.8 Prompt Reporting of SAEs to Salix Pharmaceuticals, Inc.

AESIs and SAEs must be reported promptly to the sponsor/designee once the investigator determines that the event meets the protocol definition of a AESI and/or SAE.

Prompt reporting requires:

- Completion and transmission of the AESI/SAE Report Form to the sponsor/designee via email or fax within 24 hours of the investigator's knowledge of the event. In parallel, a corresponding AE with the SAE details should be entered into the AE case report form (CRF) within 48 hours of submitting the paper form.
- Prompt reporting of additional information for previously reported AESIs/SAEs should follow the same reporting timeframe as initial reports. In addition, the corresponding AE in the AE CRF (as applicable) should be updated to ensure all data points documented in the AE CRF are aligned with the matching data points on the paper SAE Report Form.

7.9 Pregnancy Reporting

Pregnancies detected in participants assigned to study treatment should be promptly reported to the sponsor/designee via email/fax, using the Pregnancy Report Form, as soon as the investigator is notified. If a female participant becomes pregnant following assignment to study treatment, the study product will be immediately discontinued, and the participant will be followed until the outcome of the pregnancy is known. (Refer to the Section 4.4).

The sponsor/designee should be notified via email/fax of any updates on the status of the pregnancy within 24 hours by completion of a separate follow-up pregnancy notification form. Outcome of pregnancy must be reported.

Although pregnancy occurring in a clinical study is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be recorded as an AE or SAE and followed as such. If a pregnancy is associated with an SAE, an SAE Report Form should be forwarded to the sponsor/designee within 24 hours of the investigator's awareness, along with the Pregnancy Report Form.

7.10 Transmission of SAE Report Forms and Pregnancy Report Forms

Completed SAE Report Forms and completed Pregnancy Report Forms should be transmitted to the sponsor/designee via the email/fax provided below:

In North America:
ICON Drug Safety Center Americas
Phone+1 800 772 2215

Fax +1 888 772 6919
Email CHOSafety@prahs.com

In Asia Pacific:
ICON Drug Safety Center EAPA
Phone +49 621 8782 154
Fax +44 1792 525 720
Email MHGSafety@prahs.com

7.11 Contraception Requirements

All women of childbearing (reproductive) potential and all men must practice effective contraception during the study and for 30 days after the last dose.

For the purposes of this study, women who do not meet one of the following criteria listed below are considered physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
- 24 months of natural (spontaneous) amenorrhea without an alternative medical cause
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post-hysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, effective contraception is defined as use of 2 of the following for females:

- Oral contraceptives taken for at least 30 days prior to the Screening Visit.
- Placement of a non-hormonal intrauterine device or intrauterine system.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.
- Male surgical sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

For the purposes of the study, effective contraception is defined as use of one of the following for males:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up.
- The use of condoms with spermicide.

- Confirmation of birth control practiced by female partner with condom use.

True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, can be considered an acceptable method of contraception based on the evaluation of the investigator, who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

7.12 Data Monitoring Committee

7.12.1 Clinical Event Adjudication Committee

An independent, blinded central CEAC consisting of hepatologists, neurologists, and infectious disease specialists will meet to adjudicate all suspected OHE events identified either by the investigator or by periodic electronic review of reported AEs by the sponsor/designee. In addition, the CEAC will review all hospitalizations (all-cause and liver disease-related), all ED visits, hepatic decompensation events, all-cause mortality (which includes liver disease-related), and AESIs (confirmed infection). For all events identified for adjudication, the investigator will complete the appropriate modules of the eCRF and provide source documentation. Additional details are provided in the CEAC Charter.

7.12.2 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will review emerging AE and safety data. The DSMB will be separate from the Adjudication Committee and will have access to unblinded data. An independent statistician not part of the study will prepare unblinded reports for the DSMB. The DSMB (which may include sponsor personnel) and the statistician who prepares the unblinded reports will both be firewalled from sponsor personnel involved with the study. Additional details are provided in the DSMB charter.

8.0 STATISTICAL CONSIDERATIONS

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

All continuous variables will be summarized using descriptive statistics; N, mean, SD, median, maximum, and minimum. All categorical variables will be summarized using frequency counts and percentages.

Baseline value is defined as last available value prior to the first dose of study drug.

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. 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.

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

8.1 Randomization

Randomization will be stratified by country. Participants who meet the eligibility criteria and have given written informed consent will be randomized in a 1:1 allocation to 1 of 2 treatment groups as noted in Section 3.2.

8.2 Determination of Sample Size

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 participants and 20% of placebo participants will experience OHE over 48 weeks (hazard ratio of 0.472) (Bloom, 2020; Tapper, 2019; Tapper, 2020). With 2-sided Type I error rate of 0.05, and dropout rate around 10%, approximately 233 participants 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).

8.3 Analysis Populations

The analysis populations will be defined as follows:

- Intent-to-Treat (ITT) Population will include all randomized participants who have taken at least 1 dose of study drug.

- PP Population will include all participants in the ITT Population who remained in the study through end of the randomized Treatment Period and who have not deviated from the protocol in any way that is likely to seriously affect the primary outcome of the study. Important protocol deviations will be identified prior to database lock.
- Safety Population will include all randomized participants who have taken at least 1 dose of study drug.
- PK Population will include all participants in the PK substudy who have taken at least 1 dose of study drug and have sufficient data to calculate PK parameters for rifaximin and 25-desacetyl rifaximin.
- 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.
- The analyses of baseline characteristics and efficacy will be performed for the ITT Population. The primary efficacy analysis also will be performed on the PP Population as a sensitivity analysis. All safety analyses will be performed on the Safety Population.

8.4 Analysis Methods

The phrases 'statistical analysis' or 'analysis' will be used to mean inferential analysis (such as performing tests of significance, reporting p-values and CIs). When no inferential analysis will be performed, the phrases 'descriptive analysis' or 'descriptive statistics' will be used (for instance, producing summary tables of means, SDs, and percentages of responders). Primary efficacy analyses will be conducted on ITT and PP Populations using events adjudicated and confirmed to meet endpoint definitions by the CEAC. Secondary efficacy analyses will be conducted using the ITT Population.

8.4.1 Primary Efficacy Analysis

The incidence of first OHE events requiring hospitalization 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 participants with an OHE event as specified for the primary endpoint and the exposure times are the total time-on-study of all participants with or without the occurrence of OHE. Each participant'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 null hypothesis tested by the log-rank test is that of equal time distribution between rifaximin and placebo. Rejection of the null

hypothesis indicates that the event rates differ between rifaximin and placebo at 1 or more time points during the study.

H_0: $S_1(t) = S_2(t)$

versus the alternative:

H_A: $S_1(t) \neq S_2(t)$Where $S_1(t)$ and $S_2(t)$ represent the cumulative probability distributions of the times from baseline until the first OHE breakthrough for SSD-40IR and placebo arm, respectively.

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

8.4.1.1 Treatment Policy Strategy

The treatment policy estimand for the efficacy objectives in this study will be 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.

Every effort will be made to follow up with participants 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 participants who did not experience an OHE event, data will be censored at the time of their last visit.

In addition, sensitivity analyses will be performed. Worst case scenario (participants who terminated early, including death, will be treated as experiencing OHE) will be used to assess the impact of censoring. Tipping point analysis will also be conducted as an additional sensitivity analysis. The assumptions with respect to missing outcomes on the 2 treatment groups will be allowed to vary independently, and will include scenarios in which dropouts on rifaximin SSD-40IR have worse outcomes than dropouts on placebo.

8.4.1.2 Hypothetical Strategy

For hypothetical estimand, the treatment effect in the targeted population will be estimated as if all participants had continued to use assigned treatments and did not use alternative treatment. For participants who terminated early, used an alternative treatment, they will be censored at the time when the intercurrent events occur. Participants who complete the entire 72-week Treatment Period without OHE breakthrough will be censored at the end of the Treatment Period. Participants

who terminated 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 participants who did not experience an OHE event, data will be censored at the time of their last visit.

In addition, sensitivity analysis 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.

8.4.2 Secondary Efficacy Analysis

The secondary efficacy endpoint in the study is time to all-cause hospitalization.

The analysis of the time to secondary event efficacy endpoint will involve treatment group comparisons utilizing the log-rank test stratified by country. The incidence of first all-cause hospitalization 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 participants experiencing all-cause hospitalization on Days 28, 84, 140, 196, 252, etc. for each treatment group.

8.4.3 Safety Analyses

Safety evaluations will be based on the incidence, intensity and types of AEs, and changes in vital signs and clinical laboratory results.

8.4.4 Participant Disposition

Participant disposition will be summarized for all randomized participants and will include the number of participants randomized; number and percentage of participants who completed or prematurely discontinued the study, classified by reasons for premature discontinuation; the number of participants randomized at each study site; and the number and percentage of participants who completed or discontinued the study at each study site.

8.4.5 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment. Demographic characteristics include age, gender, race, ethnicity, height, and weight.

Baseline characteristics include, but are not limited to:

- MELD score and MELD-Na score
- Child-Pugh classification
- Conn score
- 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)

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.

8.4.5.1 Extent of Exposure and Treatment Compliance

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.

Calculated overall compliance will be summarized descriptively by treatment group.

8.4.5.2 Adverse Events

AEs will be coded using the MedDRA coding dictionary. TEAEs will be defined as any event with a start date occurring on or after treatment Day 1 or, if pre-existing, worsening after treatment Day 1.

The incidence of TEAEs will be summarized by body system and MedDRA PT, overall and by treatment group. If a participant reports the same AE more than once, then that participant will only be counted once for the summary of that AE, using the most severe intensity.

TEAEs will be summarized as follows:

- TEAEs
- TEAEs by intensity
- TEAEs related to study drug
- Treatment-emergent SAEs
- Treatment-emergent SAEs that led to premature discontinuation of study drug
- TEAEs that led to premature discontinuation of study
- TEAEs of infection (Infections and Infestations SOC)

All AEs, SAEs and AEs leading to premature withdrawal from the study and deaths will be listed separately.

8.4.5.3 Clinical Laboratory Assessments

Hematology, blood chemistry, coagulation, and urinalysis parameters will be summarized at baseline and at each time point, as well as changes from baseline to EOT and to EOS. Laboratory

values and changes from baseline in laboratory values will be summarized descriptively by treatment group.

A summary of shifts from baseline to final evaluation will be given for each treatment group for each parameter. The normal range for each parameter will be determined by the central laboratory and used to create categories of low, normal, or high. Any result higher than the upper limit of normal (ULN) or lower than the lower limit of normal (LLN) will be categorized as high or low respectively, and any result equal to or between the LLN and ULN will be categorized as normal. The number and percentage of participants in each treatment group in each shift category from baseline to final evaluation will be shown for each parameter.

All potentially clinically significant values for clinical laboratory tests will be assessed by the investigator. Out of range laboratory values will be flagged for review.

8.4.5.4 Ethyl Glucuronide

EtG is a direct metabolite of ethanol that is formed by enzymatic conjugation of ethanol with glucuronic acid. While alcohol is normally detected for only a few hours, EtG can be detected for 1 to 3 days. An EtG of >1000 ng/mL may indicate heavy drinking in the previous 48 hours, or light drinking the same day. An EtG from 500 to 1000 ng/mL may indicate heavy drinking in the previous 3 days, light drinking in the past 24 hours, or intense "extraneous exposure" within 24 hours. Values of <500 ng/mL may indicate heavy drinking in the previous 3 days, light drinking in the past 36 hours, or recent "extraneous" exposure.

8.4.5.5 Vital Signs

Vital sign measurements will be summarized at baseline and at each time point, as well as changes from baseline by treatment group.

8.4.5.6 Concomitant Medications

CMs will be coded using World Health Organization Drug dictionary. Medications taken during the Treatment Period will be summarized by drug class, PT, and treatment group.

8.4.5.7 Physical Examinations

Physical examination findings will be listed.

8.4.5.8 Questionnaires, Scales, and Scores

Questionnaire responses, scales, and scores will be summarized descriptively at baseline and post-baseline time points.

8.5 Statistical and Analytical Issues

8.5.1 Adjustment for Covariates

Not applicable.

8.5.2 Interim Analyses and Data Monitoring

Not applicable.

8.5.3 Multicenter Study

Statistical analyses of efficacy and safety parameters will be based upon pooled data from all study centers.

8.5.4 Exploration of the Effects of Various Prognostic Factors on Efficacy

Exploratory analyses may be performed to assess the potential impact of various prognostic factors on the primary endpoint.

8.5.5 Population Pharmacokinetics of Rifaximin

Plasma rifaximin concentrations obtained during the course of the study will be analyzed using the previously developed population PK model for rifaximin. Effects of dose strength, disease state, and other cofactors on the PK parameters may be evaluated in the model. Prior to the commencement of population pharmacokinetic analysis, an analysis plan will be generated. The analysis plan will contain details on model development, pre-specific hypotheses to be tested using the model, and simulations that will be conducted.

8.5.6 Noncompartmental Analysis of Rifaximin and 25-Desacetyl Rifaximin

Noncompartmental analysis (NCA) will be conducted for participants in the PK substudy using intensive PK samples collected at Visit 2/Day 1, Visit 3/Week 4, Visit 8/Week 36, and Visit 12/Week 68/Last Study Visit. Rifaximin and 25-desacetyl rifaximin PK parameters to be calculated include C_{max}, T_{max}, and area under the concentration-time curve from time 0 to 8 hours post-dose. PK will be summarized using descriptive statistics, including number of observations, mean, median, coefficient of variation, SD, minimum, and maximum.

8.5.7 Criteria for Stopping the Study

Not applicable.

9.0 STUDY ADMINISTRATION

9.1 Investigator Information and Training

The investigators and essential support staff will be trained by Salix or designee in regard to Good Clinical Practices (GCPs) and all aspects of protocol application and study management. It is the responsibility of the investigator to ensure training of ancillary study staff.

9.2 Monitoring

This study will be monitored by Salix or designee, in accordance with GCPs and applicable regulations. By signing this protocol, the investigator agrees to periodic, on-site monitoring of all appropriate study documentation.

The progress of the study will be monitored by periodic on-site visits and frequent communications between the sponsor or designee(s) and the investigator (either by phone, fax, email, or post).

During these contacts, the monitor will:

- Check and assess the progress of the study;
- Review study data collected;
- Conduct source document verification; and
- Identify any issues and address their resolution.

The objectives of monitoring procedures are to verify that data are authentic, accurate, and complete; that the safety and rights of participants are being protected; and that the study is conducted in accordance with the currently approved protocol (and any amendments), GCPs, and all applicable regulatory requirements.

9.3 Audits

At its discretion, Salix, or its designee, may conduct a quality assurance audit of this study. If such an audit occurs, the investigator agrees to allow the auditor direct access to all relevant documents and to schedule his/her time and the time of his/her staff to permit meetings with the auditor to discuss findings and any relevant issues.

In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the investigator agrees to allow the inspector direct access to all relevant documents and to schedule his/her time and the time of his/her staff to permit meetings with the inspector to discuss findings and any relevant issues.

10.0 ETHICAL AND LEGAL ASPECTS

The principal investigator and the study staff are responsible for conducting this study in accordance with the applicable principles which have their origins in the Declaration of Helsinki,

International Council for Harmonisation (ICH) guidelines, GCPs, and all other applicable laws and regulations.

10.1 Institutional Review Board/Ethics Committee Approval

This protocol, the informed consent, relevant supporting information and all types of participant recruitment or advertisement information must be approved by the appropriate IRB/EC before the study is initiated. Any amendments to the protocol must also be approved, where necessary, by the IRB/EC prior to implementing changes in the study. Documentation of these approvals must be provided to the sponsor prior to the initiation of the amendment.

The investigator's responsibilities regarding the IRB/EC are as follows:

- Obtaining IRB/EC approval of the protocol, informed consent, and any advertisements to recruit participants prior to their use.
- Obtaining IRB/EC approval for any protocol amendments and informed consent revisions before implementing the changes.
- Providing the IRB/EC with any required information before or during the study.
- Submitting progress reports to the IRB/EC, as required, during the conduct of the study; requesting re-review and approval of the study, as needed; providing copies of all IRB/EC re-approvals and relevant communication to the sponsor.
- Notifying the IRB/EC within 10 days (unless required sooner by IRB/EC) of all serious and unexpected AEs related to the study medications that are reported to you by the sponsor. The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The investigator must also keep the IRB/EC informed of any AEs, according to the IRB/EC policy.
- Notifying Salix within 24 hours of awareness and the IRB/EC within in 10 days (unless required sooner by IRB/EC) of all unanticipated problems involving risk to participants or others. For the purposes of this study, an unanticipated problem is defined as any incident, experience, or outcome that meets all of the following criteria:
    - Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.).
    - Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research).

- Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm).

10.2 Participant Information and Informed Consent

Informed consent will be obtained from each participant prior to conducting/obtaining any study-related assessments including the discontinuation of any study prohibited medications. An informed consent document that includes both information about the study and the consent form will be prepared and given to the participant. The document must be in a language understandable to the participant and must specify who informed the participant.

The investigator's draft ICF must be reviewed by Salix or its designee, prior to IRB/EC submission for approval. An IRB/EC-approved copy of the ICF will be forwarded to Salix or its designee. If during the course of the study, the participant's protected health information (PHI) is to be used or disclosed in a manner that is inconsistent with the informed consent that was provided, the investigator must obtain a new authorization from the participant or a waiver of authorization from the IRB/EC or privacy board, as applicable. If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/EC and use of the amended form (including for ongoing participants).

The ICF documents the study-specific information the investigator provides to the participant and the participant's agreement to participate. The investigator will fully explain in layman's terms the nature of the study, along with the aims, methods, anticipated benefits, potential risks and any discomfort participation may entail. The ICF must be appropriately signed and dated before the participant undergoes any study-related procedure. The decision regarding the participant's participation in the study that is made either by the participant or the participant's legally acceptable representative is entirely voluntary. The investigator or his/her designee must emphasize to the participant that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the participant is otherwise entitled.

The ICF shall also contain the participant's authorization for the use and disclosure of his/her PHI in connection with the study. The authorization shall include at a minimum a clear description of: the duration of the authorization, the participant's right of access to the PHI (or any suspension thereof during the course of the study), type of information to be used/disclosed in the study, the names or classes of parties that may use or disclose the PHI, the purpose of the use/disclosure of PHI, the extent of the participant's right to revoke the authorization, the extent to which participation in the study is conditioned on signing the authorization, and the potential for re-disclosure of PHI. For purposes of this study, only those participants participating in the study or the participant's legally acceptable representative(s) will be allowed to sign the ICF. This applies to all amended ICFs as well.

The original and any amended signed and dated ICFs must be retained in the participant's file at the study site; and a copy must be given to the participant or participant's legally acceptable representative(s).

10.3 Study and Site Closure or Discontinuation

Upon completion of the study, the following activities, when applicable, must be conducted by the monitor in conjunction with the investigator, as appropriate:

- Return of all study data to Salix (or designee)
- Data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused study drug and placebo
- Review of site study records for completeness

In addition, Salix reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time and for any reason. If such action is taken, Salix will discuss this with the investigator (including the reasons for taking such action) at that time. Salix will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/EC promptly and provide the reason for the suspension or termination.

10.3.1 Study Discontinuation

Should the investigator, Salix, the FDA or local regulatory authorities become aware of conditions arising during the conduct of this study that may warrant the cessation of the study, such action may be taken. Prior to such action, consultation between Salix, the investigator, and, as appropriate, the FDA and/or local regulatory authorities will take place. Conditions that may result in the termination of the study or parts thereof include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the participants enrolled in the study.
- A decision on the part of Salix to alter, suspend, or discontinue the development of the investigational product.

10.3.2 Study Site Discontinuation

The study site can be discontinued at the request of Salix, the investigator, IRB/EC, or by the FDA or local regulatory authorities. Conditions that may warrant discontinuation of the study site include, but are not limited to, the following:

- The failure of the investigator to accrue participants into the study at an acceptable rate.
- The failure of the investigator to comply with applicable current regulations and/or GCPs.
- The submission of knowingly false information from the research facility to the FDA, or other regulatory authorities.
- Insufficient adherence to protocol requirements and procedures.

If the study is prematurely discontinued, all study data must be returned to Salix or designee. In addition, the site must conduct final disposition of all used and unused study drugs in accordance with Salix procedures for the study. Study termination and follow-up will be performed in compliance with the conditions set forth in GCPs and applicable regulations. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and Salix.

10.4 Handling and Record Keeping

10.4.1 Case Report Forms and Database Processing

Participant data will be collected in an electronic case report form (eCRF) using Electronic Data Capture (EDC). The EDC system will be 21 CRF Part 11 compliant and will have a documented audit trail for all changes made to the eCRF.

The investigator or designee must enter all required participant data using the specified data collection method defined by Salix or its designee. The investigator must sign and date a declaration on the eCRF attesting to his/her responsibility for the quality of all data entered and that the data represents a complete and accurate record of each participant's participation in the study.

eCRF data will be provided to the investigator at the end of the study and will need to be retained by the investigator.

10.4.2 Source Documents

Source documents consist of, but are not limited to, inpatient hospital charts, clinic notes, out-patient records, original test results, laboratory data, worksheets, drug accountability records, consent forms, etc. Source documents must be available for review and inspection during on-site monitoring of the study by Salix, their designees, IRB/IEC, and/or regulatory authorities.

10.4.3 Participant Tracking

A drug accountability log(s), participant identification log (to be retained by the investigator only), and participant screening/enrollment data will be used to track participant participation in the study.

10.4.4 Study Files

The investigational center will maintain a specific study file. This file is participant to inspection as described under Section 9.2 and Section 9.3 of this protocol.

10.4.5 Data Management

Data management will be performed in accordance with the standard operating procedures of Salix or its designee.

10.5 Confidentiality

Anonymity of participants participating in this study will be maintained. Only participant numbers will be on any study documents submitted to the sponsor. Every effort will be made to maintain the confidentiality of documents that identify the participant by name (e.g., signed informed consent document, laboratory reports, clinic charts), except to the extent necessary to allow auditing by the FDA, or other regulatory authorities. Should the name and/or address of a participant participating in this trial be on a document submitted to the FDA, or other regulatory authorities (e.g., laboratory report), the name and/or address will be completely blocked out and replaced with the participant number.

The investigator and other study site personnel will keep confidential any information provided by Salix (including this protocol) related to this study and all data and records generated in the course of conducting the study, and will not use the information, data, or records for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or study site personnel; (2) information which it is necessary to disclose in confidence to an IRB/IEC solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study participant, or (4) study results which may be published as described in Section 10.8. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

10.6 Record Retention

Essential documents as described above should be retained for 1 of the following time periods:

- At least 2 years after the last marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region.

OR

- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of Salix to inform the investigator/institution as to when these documents no longer need to be retained.

10.7 Financing and Insurance

10.7.1 Finance

This study is supported by Salix Pharmaceuticals, Inc. an affiliate of Bausch Health US, LLC.

10.7.2 Insurance and Indemnification

Documentation of product liability insurance is on file at Salix and is available upon request.

10.8 Publication Policy

The institution and the investigator shall have the right, consistent with academic standards, to publish or present the results of the study, provided such publication or presentation does not disclose confidential information or other proprietary trade secrets of Salix. Salix will work with the protocol development team to identify a lead author for manuscript development. The manuscript authors will be determined by the amount of effort and participation each investigator contributes toward the study design, the conduct of the study and the analysis of the study data. Prior to any publication, presentation or other disclosure, institution will submit the manuscript of any proposed publication (including abstracts, or presentation to a journal, editor, meeting, seminar, or other third party) to Salix at least 60 days before publication, and Salix shall have the right to review and comment upon the proposed publication. Upon the sponsor's request, publication will be delayed up to 90 additional days to enable Salix to secure adequate intellectual property protection for Salix's property that could be affected by said publication. Salix shall have the right to require the deletion of any trade secret, or proprietary or confidential information of the sponsor. Any publication or disclosure by the institution or the investigator shall give appropriate credit to the sponsor. Where title is not retained by the publisher, title to and the right to determine the disposition of any copyrightable material, first produced or composed in the performance of the study, shall remain with the institution. With respect to such materials, the institution hereby grants to Salix an irrevocable, royalty-free, nonexclusive right to reproduce, translate, and use any such copyrighted material for its own research and commercial purposes. The investigator acknowledges and agrees that the study data and results may be disclosed by Salix to other clinical investigators, the FDA, and other regulatory authorities.

10.9 Ownership

All data and records provided by Salix Pharmaceuticals, Inc., or Bausch Health Companies Inc. and its affiliates, or generated during the study (other than a participant's medical records) and all inventions discovered during the course of conducting the study are the property of Salix. If a written agreement is executed by the parties for the conduct of the study, which includes ownership

provisions inconsistent with this statement, the ownership provisions contained in the written agreement between the parties shall control.

11.0 REFERENCES

Allampati S, Duarte-Rojo A, Thacker LR, Patidar KR, White MB, Klair JS, et al. Diagnosis of minimal hepatic encephalopathy using Stroop EncephalApp: A multicenter US-based, norm-based study. Am J Gastroenterol 2016;111:78–86. doi: 10.1038/ajg.2015.377

Amodio P, Del PF, Petteno E, Mapelli D, Angeli P, Iemmolo R, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J Hepatol 2001 Jul;35(1):37-45.

Bajaj JS, Sanyal AJ, Bell D, Gilles H, Heuman DM. Predictors of the recurrence of hepatic encephalopathy in lactulose-treated patients. Aliment Pharmacol Ther 2010 May;31(9):1012-1017.

Bass P, Dennis S. The laxative effects of lactulose in normal constipated subjects. J Gatroenterol 1981;3(Suppl 1):23-28.

Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010 Mar 25;362(12):1071-1081.

Bloom, PP, Tapper, EB. The use of administrative data to investigate the population burden of hepatic encephalopathy. Journal of Clinical Medicine 2020 Sept: 3620.

Chronic Liver Disease Foundation. Hepatic encephalopathy: A review of diagnostic methods. 2013. Jul 15.

Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy: A double blind controlled trial. Gastroenterology 1977 Apr;72(4 Pt 1):573-583.

Elfert A, Abo Ali L, Soliman S, Ibrahim S, Abd-Elsalam S. Randomized-controlled trial of rifaximin versus norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis, European Journal of Gastroenterology & Hepatology: December 2016 - Volume 28 - Issue 12 - p 1450-1454.

Everhardt J. The Burden of Digestive Diseaess in the United States. Washington, DC: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases.; 2008. Report No.: NIH Publication No. 09-6443.

Felisart J, Rimola A, Arroyo V, et al. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. Hepatology 1985;5:457-462.

Flagyl® (metronidazole) tablets [package insert]. New York, NY: G.D. Searle LLC Division of Pfizer Inc.; 2010.

Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.

Gines P, Rmola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: Results of a double-blind, placebo-controlled trial. Hepatology 1990;12:716-724.

Glaess SS, et al. Evaluation of prophylactic antibiotic regimens on recurrence and mortality in spontaneous bacterial peritonitis. Ann Hepatol (2019); 18:841-848.

Guevara M, Baccaro M, torre A, Gomez-Anson B, Rios J, Torres F, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: A prospective study with time-dependant analysis. Am J Gastroenterol 2009;104:1382-1389.

Kalaitzakis E, Simren M, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, et al. Gastrointestinal symptoms in patients with liver cirrhosis: associations with nutritional status and health-related quality of life. Scandinavian Journal of Gastroenterology 2006 Dec;41(12):1464-1472.

Kalaitzakis E, Bjornsson E. Lactulose treatment for hepatic encephalopathy, gastrointestinal symptoms, and health-related quality of life. Hepatology 2007 Sep;46(3):549-559.

Komolafe O, Roberts D, Freeman SC, Wilson P, Sutton AJ, Cooper NJ, Pavlov CS, Milne EJ, Hawkins N, Cowlin M, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis. Cochrane Database of Systematic Reviews 2020, Issue 1.

Lactulose solution [package insert]. Toronto, Ontario, Canada and Weston, FL: Apotex, Inc.; 2015.

Lv XY, Ding HG, Zheng JF, Fan CL, Li L. Rifaximin improves survival in cirrhotic patients with refractory ascites: A real-world study. World J Gastroenterol 2020; 26(2): 199-218.

Menshawy A, Mattar O, Barssoum K, AboEl-Naga A, Salim H, Mohamed A, Elgebaly A, and Abd-Elsalam S. Safety and Efficacy of Rifaximin in Prophylaxis of Spontaneous Bacterial Peritonitis: A Systematic Review and Meta-analysis. Current Drug Targets (2019) 20: 380.

Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. Gut 1982;23(1):1-7.

Mullen KD, Sanyal A, Bass NM, Poordad FF, Sheikh MY, Frederick RT, et al. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. Clinical Gastroenterology and Hepatology 2014;12:1390-1397.

National Center for Health Statistics. Summary Health Statistics: National Health Interview Survey, 2017. Public-use data file and documentation.
https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/.2018. Accessed 1 April 2019.

Navasa M, Follo A, Llovet J, et al. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. Gastroenterology 2013;111:1011-1017.

Neo-Fradin (neomycin sulfate solution) [package insert]. Big Flats, NY: X-Gen Pharmaceuticals, Inc.; 2005.

Planas R, Balleste B, Alvarez MA, Rivera M, Montoliu S, Galeras J, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 100 patients. Journal of Hepatology 2004;40(5):823-830. http://doi.org/10.1016/j.jhep.2004.01.005

Ponziani FR, Gerardi V, Pecere S, D'Aversa F, Lopetuso L, Zocco MA, Pompili M, Gasbarrini A. Effect of rifaximin on gut microbiota composition in advanced liver disease and its complications. World J Gastroenterol 2015; 21(43): 12322-12333.

Poordad F. Review Article: The burden of hepatic encephalopathy. Alimentary Pharmacology & Therapeutics 2007;25(s1):3-9.

Rimola A, Salmeron JM, Clemente G, Rodrigo L, Obrador A, Miranda ML, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: Results of a prospective, randomized, multicenter study. Hepatology 1995;21:674-679.

Romero-Gomez M. Pharmacotherapy of hepatic encephalopathy in cirrhosis. Expert Opin Pharmacother 2010 Jun;11(8):1317-1327.

Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. Hosp Pract 1987;22(1A):99, 103, 106, 110.

Runyon BA, McHutchinson JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis: A randomized controlled study of 100 patients. Gastroenterology 1991;100(6):1737-1742.

Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: An open-label randomized controlled trial of lactulose versus placebo. Gastroenterology 2009 Sep;137(3):885-891.

Singla A, Hart J, Youfu L, Tseng J, Shah S. Hospitalization for complications of cirrhosis: Does volume matter. J Gastrointest Surg 2011;15:330-335.

Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA, et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology 1992 Dec;39(6):542-545.

Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. Incidence of and risk factors for hepatic encephalopathy in a population - based cohort of Americans with cirrhosis. Hepatology Communications, Vol. 3, NO. 11, 2019.

Tapper EB, Zhao L, Nikirk S, Baki J, Parikh ND, Lok AS, Waljee AK. Incidence and bedside predictors of the first episode of overt hepatic encephalopathy in patients with cirrhosis. AM J Gastroenterol. 2020 Dec; 115 (12): 2017-2025.

Tiberi O, Tognarelli JM, Cook NA, Crossey MME, Dhanjal NS, Taylor-Robinson SD. British Journal of Hospital Medicine 2005 Nov;76(11):646-654. https://doi.org/10.12968/ hmed. 2015.76.11.646

Tito L, Rimola A, Gines P, Llach J, Arroyo V, Rodes J. Recurrence of spontaneous bacterial peritonitis in cirrhosis: Frequency and predictive factors. Hepatology 1988;8(1):27-31.

Toledo C, Salmeron JM, Rimola A, Navasa M, Arroyo V, Llach J, et al. Spontaneous bacterial peritonitis in cirrhosis: Predictive factors of infection resolution and survival in patients treated with cefotaxime. Hepatology 1993;17:251-257.

US Department of Health and Human Services, National Institutes of Health. A pocket guide for alcohol screening and brief intervention 2005 edition. http://pubs.niaaa.nih.gov/publications/Practitioner/pocketguide/pocket_guide2.htm. Accessed August 8 2019.

Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. J Gastroenterol Hepatol 2013 Mar;28(3):450-455.

Weissenborn K, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34(5):768–773.

Wright G, Jalan R. Management of hepatic encephalopathy in patients with cirrhosis. [Review] [76 refs]. Best Practice & Research in Clinical Gastroenterology 2007;21(1):95-110.

XIFAXAN® (rifaximin) tablets [US package insert]. Bridgewater, NJ: Salix Pharmaceuticals, Inc.; 10/2020.

Zafirova Z, O'connor M. Hepatic encephalopathy: Current management strategies and treatment, including management and monitoring of cerebral edema and intracranial hypertension in fulminant hepatic failure. Curr Opin Anaesthesiol 2010 Apr;23(2):121-127.

APPENDIX 1: OVERALL TIME AND EVENTS SCHEDULE

STUDY ASSESSMENTS	Screening Period	Treatment Period																		Follow-up	Unscheduled Visit
Study Visit[a]	**Visit 1**	**V2**	**V3**	**V4**	**V5**	**TC1**	**V6**	**TC2**	**V7**	**TC3**	**V8**	**TC4**	**V9**	**TC5**	**V10**	**TC6**	**V11**	**TC7**	**V12**	**V13 EOT**	**V14 EOS**	
Study Day	-28 to -1	1	28±3	56 ±3	84 ±3	112 ±3	140 ±3	168 ±3	196 ±3	224 ±3	252 ±3	280 ±3	308 ±3	336 ±3	364 ±3	393 ±3	420±3	448 ±3	476±3	504 ±3	532 ±3	
Study Week		0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	
Informed Consent	X																					
Medical History and Demographics	X																					
Confirm Eligibility (Inclusion/Exclusion Criteria)	X	X																				
Assign Subject Identification Number	X																					
Vital Signs	X	X	X	X	X		X		X		X		X		X		X		X	X	X	
12-lead Electrocardiogram in triplicate	X																					
Physical Examination	X[b]	X[c]	X[c]	X[c]	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]	X[b]	X[c]	
Serum or Urine Pregnancy Test[d]	X	X	X	X	X		X		X		X		X		X		X		X	X	X	
Hematology, blood chemistry, coagulation, and urinalysis	X	X	X	X	X		X		X		X		X		X		X		X	X	X[g]	X
Ethyl Glucuronide Test	X	X	X	X	X		X		X		X		X		X		X		X	X	X	X
Alpha-fetoprotein	X																					
Plasma PK Sample Collection (All Subjects)[e]			X								X								X			X[efg]
Plasma PK Sample Collection (PK Substudy)[f]		X	X								X								X			
Conn (WHC) Score	X	X	X	X	X		X		X		X		X		X		X		X	X	X	X

STUDY ASSESSMENTS	Screening Period	Treatment Period																		Follow-up	Unscheduled Visit
Study Visit[a]	**Visit 1**	**V2**	**V3**	**V4**	**V5**	**TC1**	**V6**	**TC2**	**V7**	**TC3**	**V8**	**TC4**	**V9**	**TC5**	**V10**	**TC6**	**V11**	**TC7**	**V12**	**V13 EOT**	**V14 EOS**	
Study Day	-28 to -1	1	28±3	56 ±3	84 ±3	112 ±3	140 ±3	168 ±3	196 ±3	224 ±3	252 ±3	280 ±3	308 ±3	336 ±3	364 ±3	393 ±3	420±3	448 ±3	476±3	504 ±3	532 ±3	
Study Week		0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	
MELD and MELD-Na	X	X	X	X	X		X		X		X		X		X		X		X	X	X	X
Child-Pugh Score and Classification	X	X	X	X	X		X		X		X		X		X		X		X	X		X
MMSE	X	X																				
SF-36		X	X	X	X		X		X		X		X		X		X		X	X		
ANT		X		X			X				X				X					X		
Caregiver Reported Burden		X	X	X	X		X		X		X		X		X		X		X	X		X
Randomization		X																				
Dispense Study Drug		X	X	X	X		X		X		X		X		X		X		X			
Collect Study Drug			X	X	X		X		X		X		X		X		X		X	X		
Record time and date of last 2 doses			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hospital admission and death data			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Dosing Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review Dosing Instructions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Adverse Events[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; ANT = Animal Naming Test; eCRF=electronic case report form; EOT=End of Treatment; MELD = Model End-Stage Liver Disease; MELD-Na = Model End-Stage Liver Disease -Sodium; MMSE = Mini-Mental State Examination; P-gp=P-glycoprotein; PK=pharmacokinetic; SAE=serious adverse event; SF-36 = Short Form-36; V = Visit; TC = Telephone Call; WHC = West Haven Criteria

a. In case of pandemic or other situation that prevents a participant from attending a post-baseline visit, a home health visit may be scheduled where possible. The home health visit may include an assessment of changes in health and medications, measurement of vital signs and body weight, safety laboratory blood and urine sample collection, collection of blood samples for PK analysis (if applicable), and checking of study medication compliance. The home health professional may also encourage the participant to complete any applicable study questionnaires via the backup website. All documented assessments and laboratory results will be reviewed by the investigator and documented in relevant eCRFs as appropriate.

b. Perform a full physical examination at screening and EOT (Visit 13). Height will only be obtained at the Screening Visit.

c. Perform a symptom-directed examination at Visits 2-12 and EOS (Visit 14), as needed. Weight will be collected at every visit.

d. Serum or urine pregnancy test is to be performed for all females of childbearing potential; a negative serum or urine test result at the Randomization Visit (Visit 2) must be documented prior to the first study drug administration.

e. For all participants, plasma samples for PK analysis will be collected at the following visits and timepoints: pre-dose at Visit 3, Visit 8, and Visit 12 (or Last Study Visit in case of participant dropout). Additionally, a plasma sample for PK analysis will be collected from any participant who receives treatment with a P-gp inhibitor, while the participant is treated with both rifaximin and the P-gp inhibitor. This sample may require an unscheduled study visit.

f. For participants in the PK substudy (approximately 10 participants per treatment group will participate in serial PK sampling at selected sites.), plasma samples for PK analysis will be collected at Visit 2 and Visit 3 at the following timepoints: pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dose; the 12-hour PK draw must be performed before administration of the next scheduled dose. For Visit 8 and Visit 12 (or Last Study Visit in case of participant dropout), only pre-dose sample will be collected.

g. AEs and SAEs will be recorded starting immediately after the participant has signed informed consent. If a participant has an SAE, a plasma sample for PK analysis will be collected as soon as feasible, and the date and time of the last 2 rifaximin doses will be recorded.

APPENDIX 2: SHORT FORM 36 HEALTH ASSESSMENT (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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SAMPLE

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

SAMPLE

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4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

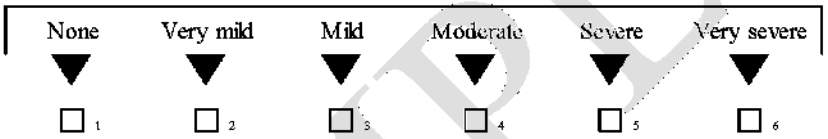
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6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



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9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

SAMPLE

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APPENDIX 3: ZARIT CAREGIVER REPORTED BURDEN

Family caregivers play an increasingly important role in health care. People experiencing acute health care problems or who require a complex regimen of treatment often depend on a family member for assistance. A fundamental element of the care process is caregivers' subjective reactions or burden. These subjective reactions indicate how well caregivers are able to manage the varied demands they face and the impact those demands are having on their lives. The Zarit Burden Inventory can be used in research to track changes over time and as a measure of treatment outcomes.

Scoring:

The Zarit Burden Inventory can be considered as a cumulative risk measure. Higher scores indicate that caregiving has greater impact on the caregiver's life. All items are scored on a 5-point scale ranging from 0 to 4. The first 21 items are scored: 0-never, 1-rarely, 2-sometimes, 3-quite frequently, and 4-nearly always. The final item, "Overall, how burdened do you feel in caring for your relative?" is scored on a comparable 5-point scale: 0-not at all, 1- a little, 2-moderately, 3-quite a bit, and 4-extremely. A total score is computed by summing the 22 items. When a few items are missing a total score can be computed by adding the mean score per item based on the items that have been answered to replace the missing items. This should not be done when the number of missing items is greater than 6.

Higher scores indicate greater burden:

Zarit Burden Inventory (ZBI-22)

Date: _____ Subject Number: _____

Visit: ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐Other

INSTRUCTIONS: The Zarit Burden Inventory can be administered by a trained interviewer or used as a paper and pencil test or with an e-version.

The following is a list of statements, which reflect how people sometimes feel when taking care of another person. After each statement, please take the time to answer each question carefully by circling the number that best represents your response. There are no right or wrong answers.

	Never	Rarely	Some-times	Quite Frequently	Nearly Always
1. Do you feel that your relative asks for more help than he or she needs?	0	1	2	3	4
2. Do you feel that, because of the time you spend with your relative, you don't have enough time for yourself?	0	1	2	3	4

3. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	0	1	2	3	4
4. Do you feel embarrassed about your relative's behavior?	0	1	2	3	4
5. Do you feel angry when you are around your relative?	0	1	2	3	4
6. Do you feel that your relative currently affects your relationship with other family members?	0	1	2	3	4
7. Are you afraid about what the future holds for your relative?	0	1	2	3	4
8. Do you feel that your relative is dependent upon you?	0	1	2	3	4
9. Do you feel strained when you are around your relative?	0	1	2	3	4
10. Do you feel that your health has suffered because of your involvement with your relative?	0	1	2	3	4
11. Do you feel that you don't have as much privacy as you would like, because of your relative?	0	1	2	3	4
12. Do you feel that your social life has suffered because you are caring for your relative?	0	1	2	3	4
13. Do you feel uncomfortable having your friends over because of your relative?	0	1	2	3	4
14. Do you feel that your relative seems to expect you to take care of him or her, as if you were the only one he or she could depend on?	0	1	2	3	4
15. Do you feel that you don't have enough money to care for your relative, in addition to the rest of your expenses?	0	1	2	3	4
16. Do you feel that you will be unable to take care of your relative much longer?	0	1	2	3	4
17. Do you feel that you have lost control of your life since your relative's illness?	0	1	2	3	4
18. Do you wish that you could just leave the care of your relative to someone else?	0	1	2	3	4
19. Do you feel uncertain about what to do about your relative?	0	1	2	3	4
20. Do you feel that you should be doing more for your relative?	0	1	2	3	4
21. Do you feel that you could do a better job in caring for your relative?	0	1	2	3	4
	Not at all	**A Little**	**Moderately**	**Quite a Bit**	**Extremely**
22. Overall, how burdened do you feel in caring for your relative?	0	1	2	3	4
Column Score					
Total Score					

Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist. 1980;20(6):649-655.

APPENDIX 4: ACLF DEFINITION

The North American Consortium for the Study of End-Stage Liver Disease defines acute-on-chronic liver failure (NACSELD-ACLF) as failure of 2 or more extrahepatic organs as follows:

Organ Failure	Definition
Brain failure	West Haven Grade 3 or 4 encephalopathy
Renal failure	Requires renal replacement therapy
Respiratory failure	Requires bilevel positive airway pressure of mechanical ventilation
Shock	Requires pressor support, a mean arterial pressure < 60 mmHg, or a reduction of > 40 mmHg in systolic blood pressure from baseline, despite adequate fluid resuscitation

Source: O'Leary JG, Reddy KR, Garcia-Tsao G, et al. NACSELD Acute-on-Chronis Liver Failure (NACSELD-ACLF) Score Predicts 30-Day Survival in Hospitalized Patients with Cirrhosis. Hepatology. 2018;67(6):2367-2374.

APPENDIX 5: CHILD-PUGH CLASSIFICATION SYSTEM

The Child-Pugh classification system for the severity of liver disease is used to determine the severity of liver disease according to the degree of ascites (via clinical assessment), serum concentrations of bilirubin and albumin, INR, and the degree of encephalopathy. The table below shows the points assigned depending on the severity of each parameter:

Parameter	**Points Assigned**		
	1	**2**	**3**
Ascites	Absent	Mild (diuretic responsive)	Moderate to Severe
Bilirubin, mg/dL	< 2	2-3	> 3
Albumin, g/dL	> 3.5	2.8-3.5	< 2.8
International Normalized Ratio	< 1.7	1.7 - 2.3	> 2.3
Encephalopathy*	None	Grade 1-2	Grade 3-4

*Encephalopathy is classified as Grade 0-4 using the Conn scoring system provided in Section 6.2.2. Between clinic visits, the highest Conn score based on participant reports of symptoms and the investigator's assessment of symptoms will be used to determine the hepatic encephalopathy component of the Child-Pugh classification at each visit.

The total score is interpreted as follows:

Grade	**Points**
A: well-compensated disease	5-6
B: significant functional compromise	7-9
C: decompensated disease	10-15

APPENDIX 6: CONN SCORE

The Conn score (also known as the West Haven Criteria) is a 5-point scale (0 to 4) for grading the severity of hepatic encephalopathy, based on neurocognitive function. A higher score indicates more severe disease.

Conn Scoring System:

Conn Score	Description
Grade 0	No personality or behavioral abnormality
Grade 1	Trivial lack of awareness, euphoria, or anxiety; shortened attention span; impairment of addition or subtraction
Grade 2	Lethargy; disorientation to time; obvious personality change; inappropriate behavior; asterixis
Grade 3	Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behavior
Grade 4	Coma; unable to test mental state

Source: Conn HO, Leevy CM, Vlahcevic ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy: A double blind controlled trial. Gastroenterology. 1977; Apr;7 2 (4 Pt 1):573-83.

APPENDIX 7: ANIMAL NAMING TEST

Instructions for Administering the ANT:

Introduction: "I'd like to ask a question to check your cognitive performance."

Instruction: "Tell me the name of as many animals as you can think of, as quickly as possible. Are you ready? Let's begin."

Procedure:

- Time for 60 seconds and record all responses.
- If the person stops before 60 seconds, say "Any more animals?"
- If the person says nothing for 15 seconds, say "A dog is an animal. Can you tell me any more animals?"

Scoring: Count the total number of animals (NOT including repetitions or non-animal words).

Source: Campagna F, Montagnese S, Ridola L, et al. The Animal Naming Test: An Easy Tool for the Assessment of Hepatic Encephalopathy. Hepatology. 2017;66(1):198-208.