1 TITLE PAGE

Clinical Study Protocol

RNHE2041

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study to Assess the Efficacy and Safety of Rifaximin Soluble Solid Dispersion (SSD) Tablets Plus Lactulose for the Treatment of Overt Hepatic Encephalopathy (OHE)

IND:	116602
Developmental phase:	Phase 2
Study design:	Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter, 5-Arm
Original Protocol:	29 March 2018
Amendment 1:	20 September 2018
Amendment 2:	05 September 2019
Amendment 3:	08 January 2020

[redacted]

Sponsor:

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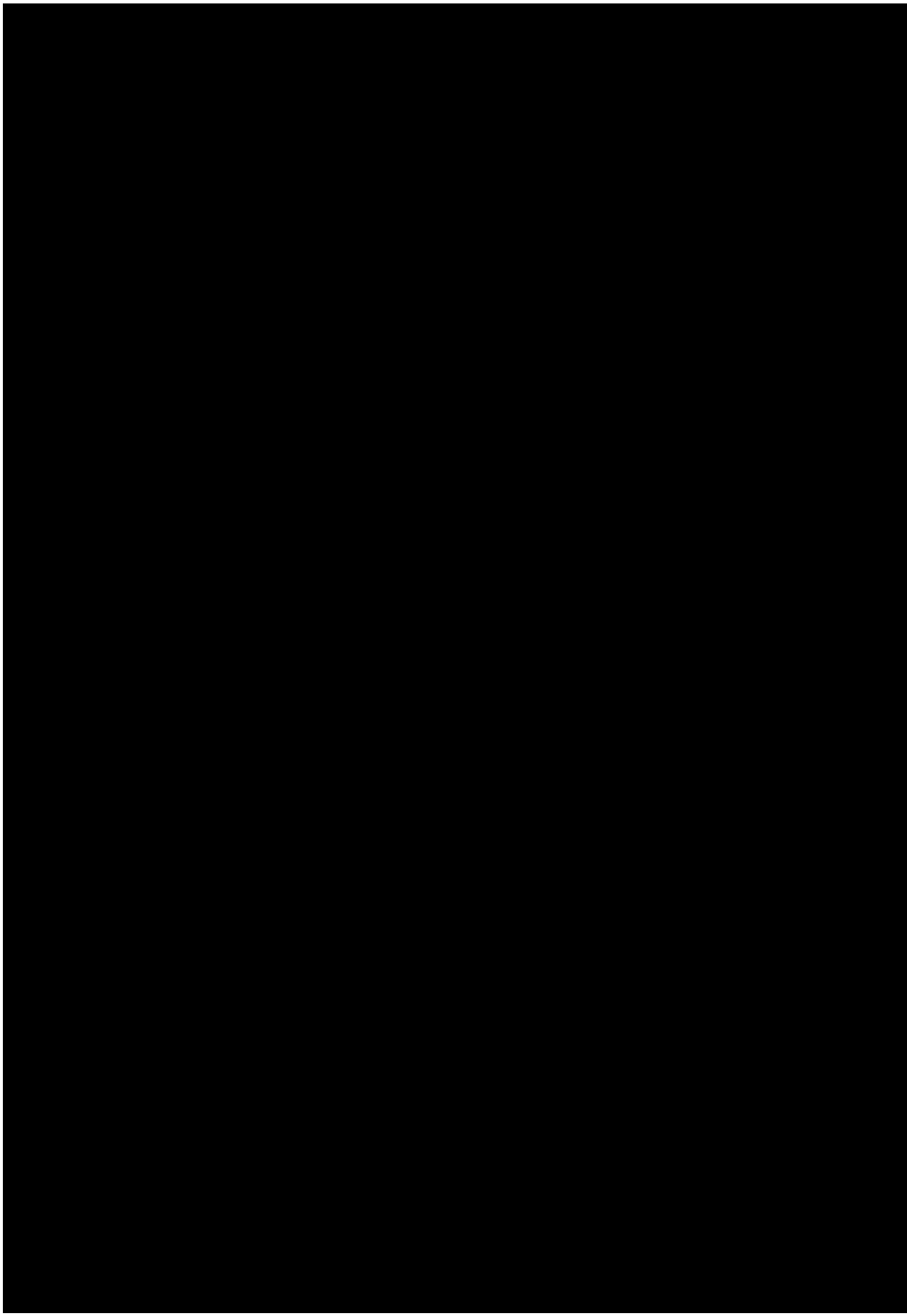

Personnel Responsible for Conducting the Study

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study to Assess the Efficacy and Safety of Rifaximin Soluble Solid Dispersion (SSD) Tablets Plus Lactulose for the Treatment of Overt Hepatic Encephalopathy (OHE)

PROTOCOL: RNHE2041

Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol, written informed consent, consent-form updates, subject-recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the investigational products(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Rifaximin Investigator Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions.

_____

Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

2.0 SYNOPSIS

Name of Sponsor/Company: Salix Pharmaceuticals, a division of Bausch Health US, LLC

Name of Investigational Product: Rifaximin SSD [40 mg immediate release (IR) and 80 mg sustained extended release (SER)] tablets

Name of Active Ingredient: Rifaximin

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study to Assess the Efficacy and Safety of Rifaximin Soluble Solid Dispersion (SSD) Tablets Plus Lactulose for the Treatment of Overt Hepatic Encephalopathy (OHE).

Number of clinical sites: Multi-center (approximately 60 US sites; expansion to ex-US countries possible)

Number of Subjects Planned: Approximately 325 subjects (65 subjects per treatment arm)

Objectives:

The primary objective of this study is to assess the efficacy of rifaximin SSD plus lactulose versus placebo plus lactulose for the treatment of overt hepatic encephalopathy (OHE).

The secondary objectives of this study are to assess the safety of rifaximin SSD in subjects with OHE and to assess the effects of treatment with rifaximin SSD on key secondary endpoints.

Endpoints:

Efficacy Phase

Primary:

- Time to OHE resolution determined using the Hepatic Encephalopathy Grading Instrument (HEGI).

Secondary:

- Time to OHE resolution defined as a West Haven Criteria (WHC) score of 0 or 1
- Time to 1 unit decrease in WHC score during the randomized treatment period.
- Change from Baseline in WHC score at Day 15 or end of blinded treatment period, whichever occurs first.
- Change from Baseline in HEGI score at Day 15 or end of blinded treatment period, whichever occurs first.
- Time to improvement in HEGI score.
- Length of hospitalization from baseline to end of blinded treatment phase.

Safety:

- Incidence of treatment-emergent adverse events (TEAEs).
- Change from baseline to OHE resolution in vital sign measurements and clinical laboratory values
- Incidence of infections, (e.g., spontaneous bacterial peritonitis (SBP), urinary tract infection, pneumonia, bacteremia, and cellulitis)

Open-label Safety Follow-up Phase:

- Reoccurrence of OHE during the 30 day follow-up period.
- Readmission to hospital during the 30 day follow-up period.
- Change from Baseline to study exit in indices of Health Outcome using the Caregiver Burden Inventory (CBI)
- Change during Follow-up Phase (from first follow-up visit post OHE resolution to study exit) in Chronic Liver Disease Questionnaire (CLDQ).

Methodology:

This is a randomized, double-blind, placebo-controlled study of Rifaximin SSD in male and female subjects hospitalized with OHE. There will be two treatment phases: (1) a safety and efficacy phase in which blinded treatment will be either (a) rifaximin SSD and lactulose or (b) placebo and lactulose; and (2) an open-label safety follow-up phase where all subjects will receive 30 days of treatment with Xifaxan® 550 mg BID.

There will be five cohorts of 65 subjects each.

- **Cohort 1 (Treatment A)** will enroll 65 subjects with OHE, to be administered 40 mg immediate release (IR) rifaximin SSD once daily (QD)* and lactulose**.
- **Cohort 2 (Treatment B)** will enroll 65 subjects with OHE, to be administered 40 mg immediate release (IR) rifaximin SSD twice daily (BID) and lactulose**.
- **Cohort 3 (Treatment C)** will enroll 65 subjects with OHE to be administered 80 mg sustained extended release (SER) rifaximin SSD once daily (QD)* and lactulose**.
- **Cohort 4 (Treatment D)** will enroll 65 subjects with OHE to be administered 80 mg sustained extended release (SER) rifaximin SSD twice daily (BID) and lactulose**.
- **Cohort 5 (Treatment E)** will enroll 65 subjects with OHE, to be administered SSD placebo twice daily (BID) and lactulose**.

All subjects who complete the blinded randomized treatment phase (defined as confirmed resolution of OHE), will continue on to the safety follow-up period receive 30 days of open-label treatment with Xifaxan® 550 mg upon hospital discharge, regardless of the treatment arm to which they were previously randomized.

An interim analysis will be conducted when at least 10 subjects per treatment group have completed participation in the blinded treatment period of the study. The unblinded interim results will be reviewed by a few designated members of the Sponsor's team who do not have direct involvement with the ongoing study. The interim results will not be shared outside of the small designated team, and no changes will be made to the ongoing study based on the interim study results.

*Blinding will be maintained in the QD SSD cohorts by administering placebo as the second daily dose. All subjects will receive two tablets per day at 12 hour (±2 hour) intervals.

** The adult, oral dosage is 2 to 3 tablespoons (30 to 45 mL, containing 20 to 30 g of lactulose) three times daily. The dosage should be adjusted to produce 2 to 3 soft stools daily or per PI discretion. Rectal lactulose may be administered in lieu of oral lactulose. Bristol stool type will still be assessed as required by the protocol for subjects dosed with rectal lactulose. Dose amount and frequency for rectal lactulose should be administered according to product label or per PI discretion.

Diagnosis and Main Criteria for Inclusion:

1. Male or female at least age 18 or older at the time of consent.
2. Females of childbearing potential, defined as a female who is fertile following menarche, must have a negative serum pregnancy test at screening and agree to use an acceptable method of contraception throughout their participation in the study. NOTE: Serum pregnancy tests performed upon hospital admission, prior to study consent, may be used at Screening.

   Note: Female subjects who have been surgically sterilized (e.g., hysterectomy or bilateral tubal ligation) or who are postmenopausal (defined as total cessation of menses for > 1 year) will not be considered "female subjects of childbearing potential".
3. Subject is hospitalized with encephalopathy secondary to liver cirrohis and has a confirmed diagnosis of OHE at Baseline. .
4. Subject has a Grade 2 or Grade 3 HE episode according to the HE Grading Instrument (HEGI) following: a) at least one lactulose treatment with subsequent bowel movement(s) and b) be adequately hydrated (IV fluids at PI discretion).

5. Surrogate decision maker must be able to read, understand and provide written informed consent on behalf of the subject on the Institutional Review Board (IRB)/Ethics Committee (EC) approved ICF and provide authorization as appropriate per local privacy regulations.
6. Subject must be able to swallow oral medication (e.g., study drug) without assistance at Baseline.

Key Exclusion Criteria:

1. Subject has an uncontrolled major psychiatric disorder including major depression or psychoses as determined by the investigator.
2. Subject has sepsis, as determined by the investigator.
3. Subject is currently taking oral antibiotics, which cannot be discontinued or changed to parenteral at time of enrollment. Note: Subjects currently taking rifaximin who discontinue use at time of enrollment are not excluded.
4. Subject shows presence of intestinal obstruction or has inflammatory bowel disease.
5. Subject has uncontrolled Type 1 or Type 2 diabetes as determined by the investigator. Note: Subjects with controlled diabetes may be enrolled if they are on stable doses of insulin or oral hypoglycemic drugs for at least 3 months prior to screening, and demonstrate clinically acceptable blood glucose control at Baseline, as determined by the investigator.
6. Subject has an active malignancy (exceptions: non-melanoma skin cancers).
7. Subject has HCC (Hepatocellular carcinoma) , history of HCC, or reasonable clinical suspicion of HCC per PI. Prior imaging completed within 6 months prior to obtaining consent may be used to rule out HCC. In lieu of recent imaging, if AFP is above the upper limit of normal cross-sectional imaging techniques should be used to rule out HCC.
8. Subject has any condition or circumstance, determined by the investigator, (including alcohol or substance abuse) that adversely affects the subject or could cause noncompliance with treatment, or may affect the interpretation of clinical data, or may otherwise contraindicate the subject's participation in the study.
9. If female, subject is pregnant, at risk of pregnancy, or is nursing.
10. Known human immunodeficiency virus (HIV) infection.
11. Subject has undergone a liver transplant within 5 years prior to Baseline.
12. Subject is an employee of the site that is directly involved in the management, administration, or support of this study or is an immediate family member of the same.
13. Subject has a history of hypersensitivity to rifaximin, rifampin, rifamycin antimicrobial agents, or any of the components of rifaximin SSD.
14. Subject used any investigational product or device within 30 days or 5 drug half-lives (whichever is longer) prior to baseline.
15. Subject used milk thistle or any known P-gp inhibitor within 30 days prior to Baseline.

Investigational product, dosage and mode of administration:

- Treatment A: 40 mg immediate release (IR) rifaximin SSD tablet once daily (QD) and lactulose*.
- Treatment B: 40 mg immediate release (IR) rifaximin SSD tablet twice daily (BID) and lactulose*.
- Treatment C: 80 mg sustained extended release (SER) rifaximin SSD tablet once daily (QD) and lactulose*.
- Treatment D: 80 mg sustained extended release (SER) rifaximin SSD tablet twice daily (BID) and lactulose*.
- Treatment E: SSD placebo tablet twice daily (BID) and lactulose*.

* The adult, oral dosage is 2 to 3 tablespoons (30 to 45 mL, containing 20 to 30 gm of lactulose) three times daily (TID). The dosage must be adjusted to produce 2 to 3 soft stools daily or per PI discretion. Rectal lactulose may be administered in lieu of oral lactulose. Bristol stool type will still be assessed as required by the protocol for subjects dosed with rectal lactulose. Dose amount and frequency for rectal lactulose should be administered according to product label or per PI discretion.

Duration of treatment:

Subjects will be on treatment for up to 14 days in the blinded, placebo-controlled portion of the study. Subjects who continue on to the open-label phase will receive 30 days of open-label treatment with Xifaxan® 550 mg upon hospital discharge, regardless of the treatment arm to which they were randomized.

Criteria for Evaluation:

The primary endpoint in this study is time to resolution of OHE per the HE Grading Instrument (HEGI). OHE status will be evaluated every 12 hours (+/- 2 hours) after randomization. Resolution is defined as a HEGI score < 2.

Statistical Methods:

The primary efficacy endpoint is time to OHE resolution. OHE resolution is defined as a HEGI score < 2. Time to resolution of OHE is defined as the duration between the date/time of first dose of study drug and the date/time of first resolution of OHE. Subjects who complete the blinded randomized treatment period without experiencing OHE resolution will be censored at 14 days post first dose.

The primary efficacy analysis of time to OHE resolution between each active rifaximin SSD plus lactulose treatment group and the placebo plus lactulose group will be tested using the log-rank test.

Analysis of primary efficacy endpoint will be tested in intent-to-treat (ITT) and per protocol (PP) populations.

- The ITT population will include all randomized subjects who received at least one dose of blinded treatment drug.
- The PP population will include all ITT subjects who remain in study through the end of the blinded 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 incidence of treatment-emergent AEs will be summarized for each treatment group by body system and MedDRA preferred term. If a subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE, using the most severe intensity.

The incidence of treatment-emergent AEs of infections, such as spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), pneumonia, bacteremia and cellulitis, will be summarized by each treatment group. If a subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE, using the most severe intensity. Severity and AE leading to early termination will also be presented for these infection AEs.

On-study vital signs assessment will include supine blood pressure (systolic and diastolic), pulse rate, respiration rate, and weight and temperature. Vital signs will be summarized at baseline and at each time point collected, as well as changes from baseline. For each summary, the N, mean, median, standard deviation (SD), minimum, and maximum values will be given by treatment group. Pretreatment vital signs obtained closest in time to first dose of study drug will be used for summarization and analysis of baseline and change from baseline.

Similarly, on-study clinical labs will be summarized at baseline and at each time point collected.

Sample Size:

Approximately 325 subjects will be randomized in a 1:1:1:1:1 ratio to rifaximin SSD tablets (40 mg immediate release (IR), QD plus lactulose; 40 mg immediate release (IR), BID plus lactulose; 80 mg sustained extended release (SER), QD plus lactulose; 80 mg sustained extended release (SER), BID plus lactulose, and placebo, BID plus lactulose).

The sample size estimation is based on cumulative probability distributions of the time from baseline until the first OHE resolution (HEGI score < 2) between treatment groups using the log-rank test.

This sample size estimation is based on a previous study with rifaximin (Sharma 2013). It is assumed that approximately 76% of rifaximin plus lactulose subjects and 51% of placebo plus lactulose subjects will experience OHE resolution over the course of up to 14 days of treatment. With two-sided type I error rate of 0.05, approximately 61 evaluable subjects per treatment group will provide at least 80% power to demonstrate the superiority of rifaximin SSD to placebo using the log-rank test.

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List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition or Explanation
AASLD	American Association for the Study of Liver Disease
AE	Adverse event
AFP	Alpha-fetoprotein
AUC	Area under the plasma concentration-time curve
AUC_t	Area under single-dose concentration-time curve
AUC_{0-t}	Area under single-dose concentration-time curve from time 0 to time of last detectable concentration at time (t) [amount·time/volume]
$AUC_{0-\infty}$	Area under single-dose concentration-time curve from time 0 to infinite time post dose [amount·time/volume; concentration time]
BID	Twice a day
BT	Bacterial translocation
CBI	Caregiver Burden Inventory
CLD	Chronic liver disease
CLDQ	Chronic liver disease questionnaire
C_{max}	Maximum drug concentration
CRF	Case report form
DR	Delayed-release
EASL	European Association for the Study of the Liver
EC	Ethics Committee
EIR	Extended intestinal release
EOS	End of study
EOT	End of treatment
EVB	Esophageal variceal bleeding
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HEGI	Hepatic encephalopathy grading instrument
HIV	Human Immunodeficiency Virus
HRS	Hepatorenal syndrome
Hz	Hertz
IBO	Intestinal bacterial overgrowth
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate release
IRB	Institutional Review Board
IV	Intravenous
MELD	Model for End-stage Liver Disease
MMP-9	Matrix metalloproteinase-9

Abbreviation or Term	Definition or Explanation
NIS	Nationwide Inpatient Sample
OHE	Overt Hepatic Encephalopathy
PXR	Pregnane X receptor
QD	Once a day
QHS	Every bedtime
QoL	Quality of Life
SAE	Serious Adverse Event
SBP	Spontaneous bacterial peritonitis
SER	Sustained Extended Release
SOP	Standard Operating Procedure
SSD	Soluble Solid Dispersion
TEAE	Treatment Emergent Adverse Event
TID	Three times a day
TIPS	Transjugular intrahepatic portosystemic shunt
T_{max}	Time taken to reach C_{max}
US	United States

3.0 INTRODUCTION

3.1 Disease Background and Scientific Rationale

3.1.1 Liver Cirrhosis

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 2.6 million people have liver disease in the US (Pleis 2009). In 2004, 2.3 million ambulatory care visits, and 759,000 hospitalizations were needed to care for these patients (Everhart 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 (NIS) 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% to 50% (Toledo 1993, Runyon 1991, Rimola 1995, Felisart 1985, Navasa 2013, Gines 1990, Tito 1988, Planas 2004). The incidence of cirrhosis in the US is on the rise and will continue to be a major health burden. The NIS database indicated that cases of cirrhosis increased at an annual rate of 3.7% over the 9-year period studied. It is predicted that over the next 20 years, cases of Hepatitis C Virus (HCV)-related cirrhosis will double (Davis 2010). This is not unexpected given the current prevalence of chronic HCV infection in the US is 2.7 to 3.9 million people and the fact that the cause of cirrhosis is HCV infection in approximately 26% of cases (Wolf 2012).

3.1.2 Pathophysiology of Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a major complication of cirrhosis and the result of a cascade of events that begins with hepatocyte death. Hepatocyte death results in inflammation and fibrosis of the hepatic architecture.

Hepatic encephalopathy (HE) is a reversible neuropsychiatric abnormality that presents in 30% to 45% of patients with cirrhosis and in 10% to 50% of patients with a transjugular intrahepatic portosystemic shunt (TIPS) (Poordad 2007, Amodio 2001, Guevara 2009). Alterations in the production, metabolism, and excretion of nitrogenous compounds, including ammonia, contribute to the pathogenesis of HE. Ammonia is a by-product of nitrogen metabolism. Approximately half of the body's ammonia is produced in the portal-drained viscera, and half is produced in the colon.

Ammonia is primarily metabolized in the liver to urea and excreted in the urine. In patients with liver disease, this function is diminished or lost, and the skeletal muscle becomes a major elimination pathway. Cirrhotic patients are often muscle wasted, and this can lead to toxic accumulation of ammonia. Metabolism of ammonia in astrocytes in the brain can have both excitatory and inhibitory effects on neurotransmission and causes the common clinical signs of HE including confusion, coma, asterixis, loss of fine motor skills, hyperreflexia, and slow, monotonous speech. 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 include gastrointestinal (GI) bleeding, dehydration, excess dietary protein intake, hypokalemic alkalosis, infection, and constipation. Central benzodiazepine receptors also appear to be upregulated in the presence of ammonia, making patients with cirrhosis more sensitive to the effects of benzodiazepines (Schiano 2010).

3.2 Current Therapy for Major Complications of CLD

The management of cirrhosis and its complications (including HE) is based on disease severity and whether or not complications have developed (i.e., decompensated disease). The American Association for the Study of Liver Disease (AASLD) Practice Guidelines for evaluating patients for liver transplantation recommend that patients with cirrhosis should be evaluated for transplant when they develop evidence of liver dysfunction defined by a Child- Pugh score of ≥ 7 and model for end-stage liver disease (MELD) score ≥ 10 (Murray 2005). In 2010, a set of quality indicators for use in the management of cirrhosis was developed by an 11-member panel of specialists from across the US. This panel recommended that patients with a MELD score of ≥ 15 or ≤ 15, with complications, be referred to a transplant center (Starr 2011).

The development of esophageal variceal bleeding (EVB), ascites, SBP, HE, or HRS has a profound impact on prognosis. Despite current medical therapies for EVB, ascites, SBP, and HE, patients with compensated disease who develop 1 of these complications have a 5-year survival rate of 20% to 50% (Gines 1987, Fattovich 1997). The survival rate of patients who develop SBP or HRS is particularly poor. For SBP, less than half will survive 1-year; the median survival rate for patients with type I HRS is less than 2 weeks (Andreu 1993; Gines 1993).

As noted previously for data prior to 2010, HE presents in 30% to 45% of patients with cirrhosis and in 10% to 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 (Gines 1993, Romero-Gomez 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 to 3 soft stools per day to achieve efficacy (Lactulose Solution PI). Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy (i.e., HE). HE treatment guidelines from the AASLD/European Association for the Study of the Liver (EASL) recognize that putting patients on maintenance therapy with lactulose may not be enough to prevent recurrences. A previous study (Sharma 2013) demonstrated that a combination of rifaximin plus lactulose was more effective than lactulose alone for improvement of HE and reduction in mortality.

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 (Bajaj 2010; Bass 2007; 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 g to 12 g. However, neomycin use is only recommended for short-term therapy in the treatment of HE due to the risk of nephrotoxicity and ototoxicity (Neo-Fradin PI®). Although oral neomycin is commonly considered a nonabsorbed 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 (Neo-Fradin PI®). 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 (Flagyl (metronidazole) capsules [package insert]).

3.3 Clinical and Non-clinical Information

3.3.1 Clinical Experience with Rifaximin Soluble Solid Dispersion Tablets

The pharmacokinetics of rifaximin were evaluated in four Phase 1 studies and one Phase 2 study after administration of the rifaximin soluble solid dispersion (SSD) formulation in either healthy volunteers or subjects with impaired liver function.

Study RFPK1042 was a 2-part study evaluating the pharmacokinetics of rifaximin SSD at different doses and the regional absorption and bioavailability of rifaximin following targeted release at prespecified locations in the GI tract. Study RNPK1002 evaluated the pharmacokinetics 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 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 subjects with mild, moderate, and severe hepatic impairment and in healthy subjects. Study RNLC2131 evaluated the population pharmacokinetics of rifaximin SSD tablets in subjects 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 subjects 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 Cmax values ranged from 1.41 ng/mL to 5.20 ng/mL [for the sustained extended release (SER) and immediate release (IR) formulations, respectively]; corresponding mean AUC0-∞ values were 10.2 ng.h/mL and 24.9 ng.h/mL (RNPK1002 CSR, Table 6). Compared with the current 550 mg tablet formulation, rifaximin IR and SER tablet formulations provide similar or lower Cmax and AUC values systemically, accompanied by prolonged half-lives that may indicate increased GI residence times. The data demonstrate the feasibility of a single daily rifaximin IR or SER dose.

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 subjects with early decompensation) and safety of rifaximin SSD tablets in subjects with early decompensated liver cirrhosis. Subjects with documented medically non-refractory ascites who had not previously experienced spontaneous bacterial peritonitis (SBP), esophageal variceal bleeding (EVB), or hepatorenal syndrome (HRS) were enrolled in the study. Subjects completed a 1 to 21-day Screening Period, a 24-week Treatment Period, and a 2-week Follow-up Period. A total of 518 subjects 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).

Subjects 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 MELD score was 11.5, with the majority of subjects (280 subjects; 54.3%) scoring between 11 and 18. The overall mean MELD score was 12.9, with the majority of subjects (327 subjects; 63.4%) again scoring between 11 and 18. Most subjects (416 subjects; 80.6%) had a class B Child-Pugh classification and a Conn score category of 0 (317 subjects; 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 subjects; 46.9%) with "alcoholic liver disease" reported as the second most common (220 subjects; 42.6%). The majority of subjects did not have HE or diabetes at Screening (364 subjects; 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 subjects 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 CSR Appendix 16.1.13). In addition, subjects 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, subjects 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 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, subjects 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, SAEs, severe TEAEs, and drug-related TEAEs occurred most frequently in the GI disorder System Organ Class (SOC).

Hepatic encephalopathy 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.

3.4 Rationale

3.4.1 Scientific Rationale for the Use of Rifaximin in Preventing Major Complications of Liver Cirrhosis:

Multiple lines of clinical and experimental evidence support the use of rifaximin in preventing complications of cirrhosis through mechanisms that:

- decrease serum neurotoxin production
- decrease endotoxin production and absorption
- reduce intestinal bacterial translocation (BT)
- reduce intestinal permeability
- decrease portal venous pressures through reduction in endotoxin concentrations
- activate the nuclear pregnane X receptor (PXR)

Rifaximin is a nonaminoglycoside, semisynthetic antibiotic derived from rifamycin. It is a non-systemic, poorly-absorbed, oral antibiotic specific for enteric pathogens of the GI tract (Xifaxan® PI, Gerard 2005, Gillis 1995, Hoover 1993). Rifaximin has potentially important advantages in preventing the complications of cirrhosis relative to orally bioavailable, broad-spectrum antibiotics. For example, rifaximin has minimal systemic exposure regardless of food intake or presence of GI disease which mitigates the risk of systemic side effects. Neither a reduction in overall colonic bacteria nor an increase in antimicrobial resistance in the colonic bacteria occurs to a clinically significant extent.

Furthermore, in vitro studies have demonstrated that rifaximin interferes with the transfer of and promotes the elimination of plasmids from various Gram-positive and Gram-negative bacterial hosts, suggesting that rifaximin is capable of limiting the transfer of antibiotic-resistance plasmids and the diffusion of virulence factors in bacteria (Debbia 2008).

The use of rifaximin in the treatment of complications of cirrhosis is supported by microbiological and pharmacodynamic evidence which suggests both effects on bacteria and on host inflammatory response as mechanisms of action as outlined below:

Rifaximin is active against the bacteria that have been investigated as possible pathogenic agents for SBP (Xifaxan® PI, Gerard 2005, Gillis 1995, Hoover 1993).

Rifaximin affects bacterial translocation to mesenteric lymph nodes (Fiorucci, 2002).

Rifaximin induces in enteroaggregative and enterotoxigenic *Escherichia coli* a loss of virulence factors such as enterotoxins, surface adhesion factors and matrix metalloproteinase-9 (MMP-9), and changes in epithelial cell physiology associated with reduction in bacterial attachment/internalization (Brown 2010; Fiorucci 2002).

Data indicate that the anti-inflammatory activity of rifaximin is due to its gut-specific human PXR activation (Ma 2007). Activation of PXR, such as that observed with rifaximin in the intestinal lumen, results in upregulation of metabolic enzymes and transporters (e.g., CYP3A, sulfotransferases, and P-glycoprotein) that may result in increased epithelial cell protection against bacterial metabolic products.

3.4.2 Study Rationale

Cirrhosis is a major cause of CLD in the US and is the 12th leading cause of death. The incidence of cirrhosis in the US is increasing and will continue to be a major health burden from an economic and societal/caregiver perspective. While liver transplant is the only curative therapy for cirrhosis; safe, effective, and cost-efficient therapies for the prevention of the major complications of cirrhosis including mortality, and to bridge a patient to transplant are needed. These therapies must arrest the hemodynamic and infectious etiologies of cirrhosis complications, and improve the morbidity, mortality, and quality of life of the patient.

Rifaximin is approved by the United States Food and Drug Administration (FDA) to reduce the risk of OHE recurrence in patients ≥ 18 years of age. It is not indicated for primary prophylaxis of HE events.

The current literature supports the potential therapeutic utility of rifaximin in treating complications of cirrhosis with ascites such as SBP, HE, EVB, and HRS through multiple mechanisms including direct suppression of intestinal bacterial overgrowth (IBO) and bacterial translocation (BT) that leads to a reduction in endotoxemia, bacteremia, and bacterial seeding of ascitic fluid, and indirect improvement in portal hemodynamics. 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.

The new rifaximin SSD IR and SER are novel formulations of rifaximin that are designed to improve luminal solubility to increase the availability of soluble rifaximin to the gut lumen and epithelia, while minimizing systemic exposure. Its unique formulation greatly improves its water solubility without the need for bile acids, an important determination of solubility of the current approved formulation (Darkoh 2010).

This characteristic makes the new SSD formulation particularly attractive for use in a population with significantly impaired hepatic function. Data from early phase trials with the SSD formulation support the safety, solubility and potential clinical utility of rifaximin in preventing complications of cirrhosis in patients with early liver decompensation. Based on these data and the medical need for safe and effective treatments for OHE, the Sponsor is seeking to initiate clinical development of Rifaximin SSD in OHE.

The current standard of care for patients with hepatic encephalopathy is treatment with nonabsorbable disaccharides lactulose or lactitol, which decreases the absorption of ammonia through cathartic effects and by altering colonic pH. In addition to lactulose, oral antibiotics have been used in OHE to reduce ammonia-producing enteric bacteria. However, because of side effects these agents are only infrequently used at present.

Rifaximin is currently approved for reduction in risk of OHE recurrence, but not for the treatment of OHE. Randomized clinical trials showing the superiority of rifaximin plus lactulose versus lactulose alone suggest that rifaximin may be useful in the treatment of OHE. Based on these data and the need for safe and effective alternatives to systemic broad spectrum antibiotics used to treat complications of cirrhosis, this Phase 2 dose-ranging trial will be conducted to assess the viability of rifaximin SSD for the prevention of complications in cirrhosis patients with early decompensation.

4.0 OBJECTIVES

4.1 Efficacy Objectives

4.1.1 Primary Objective

The primary objective of this study is to assess the efficacy of rifaximin SSD [40 mg immediate release (IR) and 80 mg sustained extended release (SER)] plus lactulose versus placebo plus lactulose for the treatment of OHE.

4.1.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess the safety of rifaximin SSD in subjects with OHE.
- Assess the effects of treatment with rifaximin SSD on key secondary endpoints.

5.0 STUDY DESIGN

5.1 Description of Study Design

Study RNHE2041 is 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 subjects hospitalized with OHE. Subjects who have liver cirrhosis and OHE, defined as a score of 2 or 3 on the Hepatic Encephalopathy Grading Instrument [(HEGI); Appendix A], are eligible for enrollment. Subjects who successfully meet the inclusion/exclusion criteria will enter the treatment period and will be randomized in a 1:1:1:1:1 ratio into 1 of 5 treatment groups as noted below. The blinded treatment period starts upon randomization following hospital admission. Subjects will be on blinded treatment for up to 14 days. All subjects who complete the blinded randomized treatment phase (defined as confirmed resolution of OHE), will continue on to the safety follow-up period and receive 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 subjects remain hospitalized following OHE resolution, standard of care treatment (which may include Xifaxan® 550 mg) should be given until hospital discharge. Open-label drug should only be dispensed to subjects upon hospital discharge. Please note this may be on a different day than OHE resolution.

- Treatment A: 40 mg immediate release (IR) rifaximin SSD tablet once daily (QD) and lactulose*.
- Treatment B: 40 mg immediate release (IR) rifaximin SSD tablet twice daily (BID) and lactulose*.

- Treatment C: 80 mg sustained extended release (SER) rifaximin SSD tablet once daily (QD) and lactulose*.
- Treatment D: 80 mg sustained extended release (SER) rifaximin SSD tablet twice daily (BID) and lactulose*.
- Treatment E: SSD placebo tablet twice daily (BID) and lactulose*.

*Oral Lactulose will be administered according to the product label, with dosage adjusted to produce 2 to 3 soft stools daily or per PI discretion. Rectal lactulose may be administered in lieu of oral lactulose. Bristol stool type will still be assessed as required by the protocol for subjects dosed with rectal lactulose. Dose amount and frequency for oral and rectal lactulose should be administered according to the product label or per PI discretion.

An interim analysis will be conducted when at least 10 subjects per treatment group have completed participation in the blinded treatment period of the study. The unblinded interim results will be reviewed by a few designated members of the Sponsor's team who do not have direct involvement with the ongoing study. The interim results will not be shared outside of the small designated team, and no changes will be made to the ongoing study based on the interim study results.

5.2 Selection of Study Population

Approximately 325 subjects (65 subjects per arm), from approximately 60 study sites in the US, hospitalized for liver cirrhosis and OHE, with a HEGI score of 2 or 3 following adequate hydration and lactulose treatment, will be enrolled in this clinical investigation. Expansion to other countries may be considered.

5.2.1 Eligibility

5.2.1.1 Inclusion Criteria

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

1. Male or female at least age 18 or older at the time of consent.
2. Female subjects of childbearing potential, defined as fertile following menarche, must have a negative serum pregnancy test at screening and agree to use an acceptable method of contraception throughout their participation in the study. NOTE: Serum pregnancy tests performed upon hospital admission, prior to time of consent, may be used at Screening. Acceptable methods of contraception include double barrier methods (condom with spermicidal jelly or a diaphragm with spermicide), hormonal

methods (e.g., oral contraceptives, patches or medroxyprogesterone acetate), or an intrauterine device (IUD) with a documented failure rate of less than 1% per year. Abstinence or partner(s) with a vasectomy may be considered an acceptable method of contraception at the discretion of the investigator. See Section 5.2.2 for additional information.

Note: Female subjects who have been surgically sterilized (e.g., hysterectomy or bilateral tubal ligation) or who are postmenopausal (defined as a total cessation of menses for > 1 year) will not be considered "female subjects of childbearing potential".

3. Subject is hospitalized with encephalopathy secondary to liver cirrohis and has a confirmed diagnosis of OHE at Baseline. .
4. Subject has a Grade 2 or Grade 3 HE episode according to the HEGI (Appendix A) following: a) at least one lactulose treatment with subsequent bowel movement(s) and b) be adequately hydrated (IV fluids at PI discretion).
5. Surrogate decision-maker must be able to read, understand, and provide written informed consent on behalf of the subject on the Institutional Review Board (IRB)/Ethics Committee (EC) approved ICF and provide authorization as appropriate per local privacy regulations.
6. Subject must be able to swallow oral medication (e.g., study drug) without assistance at Baseline.

5.2.1.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria are met:

Current or Past Medical History

1. Subject has an uncontrolled major psychiatric disorder including major depression or psychoses, as determined by the investigator (Diagnostic and Statistical Manual of Mental Disorders, 5th., American Psychiatric Association, 2013).
2. Subject has sepsis, as determined by the investigator.
3. Subject is currently taking oral antibiotics, which cannot be discontinued or changed to parenteral at time of enrollment. Note: Subjects currently taking rifaximin who discontinue use at time of enrollment are not excluded.
4. Subject shows presence of intestinal obstruction or has inflammatory bowel disease.

5. Subject has uncontrolled Type 1 or Type 2 diabetes as determined by the investigator. Note: Subjects with controlled diabetes may be enrolled if they are on stable doses of insulin or oral hypoglycemic drugs for at least 3-months prior to screening, and demonstrate clinically acceptable blood glucose control upon admission in the opinion of the investigator.
6. Subject has an active malignancy (exceptions: non-melanoma skin cancers).
7. Subject has HCC, history of HCC, or reasonable clinical suspicion of HCC per PI. Prior imaging completed within 6 months prior to obtaining consent may be used to rule out HCC. In lieu of recent imaging, if AFP is above the upper limit of normal cross-sectional imaging techniques should be used to rule out HCC..
8. Subject has any condition or circumstance, as determined by the investigator, (including alcohol or substance abuse) that adversely affects the subject or could cause noncompliance with treatment, or may affect the interpretation of clinical data, or may otherwise contraindicate the subject's participation in the study.
9. If female, subject is pregnant, at risk of pregnancy, or is nursing.
10. Known human immunodeficiency virus (HIV) infection.
11. Subject has undergone a liver transplant within 5 years prior to Baseline.
12. Subject is an employee of the site that is directly involved in the management, administration, or support of this study or is an immediate family member of the same.
13. Subject has a history of hypersensitivity to rifaximin, rifampin, rifamycin antimicrobial agents, or any of the components of rifaximin SSD.
14. Subject used any investigational product or device within 30 days or 5 drug half-lives (whichever is longer) prior to Baseline.
15. Subject used milk thistle or any known P-gp inhibitor within 30 days prior to Baseline.

Subject Withdrawal Criteria

All premature discontinuations and their reasons must be carefully documented by the investigator on the final eCRF, and if need be, on the AE form. Reasons for study completion/discontinuation as listed on the report form are described as follows:

- **Normal Study Completion** – subject completes study as planned per the protocol
- **Adverse Event** – complete AE form

- **Subject Request** – consent withdrawal (i.e. subject moved, schedule conflicts)
- **Protocol Violation** – contact the Sponsor or Sponsor's designee prior to making decision
- **Lost to Follow-Up** – document with two phone calls and a certified letter
- **Pregnancy** – subject will discontinue study drug immediately, but will be followed to term; pregnancy form must be completed
- **Worsening Condition** – subject requires alternate treatment prior to completing the study and the investigator determines it is not due to lack of efficacy (i.e. requires liver transplant during the study).
- **Other** – specify in the comments section of final eCRF

Subjects who terminate treatment early will be asked to complete all end of study visit assessments (see Section 8.3.1 for additional information) prior to commencement of any alternative medication or therapy (if possible). Subjects who discontinue from the study during the treatment period will be asked to come back for the 30 day post-treatment cessation follow-up visit.

All subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice. No constraints will be placed on ordinary subject management, and subjects, when appropriate, will be placed on other conventional therapy upon request or whenever clinically necessary as determined by their physician.

5.2.2 Female Subjects of Childbearing (Reproductive) Potential

Rifaximin is a Pregnancy Category C drug with no adequate and well controlled studies in pregnant women, and has been shown to be teratogenic in rats and rabbits at doses that caused maternal toxicity. Please refer to the Rifaximin Investigator Brochure and Xifaxan® complete prescribing information for additional information on rifaximin (Xifaxan® PI).

Female study subjects of childbearing (reproductive) potential must have a negative serum pregnancy test at Screening and agree to use an acceptable method of contraception throughout their participation in the study (see details in Section 5.2.1.1, Inclusion Criteria). If a female subject becomes pregnant while on this study, the study drug will be immediately discontinued and the subject will be followed until the outcome of the pregnancy is known. The pregnancy will be reported to the Sponsor using the guidelines provided in Section 9.9 and Section 9.10.

5.3 Investigators

The study will be conducted at approximately 60 investigative sites. The study will be conducted by Investigators who are determined by the Sponsor to be suitably qualified by training and experience to conduct this study in compliance with all applicable ICH GCPs guidelines and FDA Federal Regulations or Local Regulations.

In the event that the participating sites do not meet full enrollment in a timely manner, the Sponsor may decide to increase enrollment at other active participating sites and/or activate additional site(s) as needed to satisfy the enrollment requirements of the study.

5.4 Study Duration

Subjects will be enrolled in the double-blind, placebo-controlled phase during hospitalization, up to 14 days, and in the open-label, safety follow-up phase for 30 days.

5.5 Treatments

In the double-blind phase, subjects will be randomized (1:1:1:1:1) to the following treatment groups:

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

* Blinding will be maintained in the QD SSD cohorts by administering placebo as the second daily dose. All subjects will receive two tablet per day at 12-hour (±2 hour) intervals based on the time of the first dose following randomization.
** The adult, oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 to 30 gm of lactulose) TID. The dosage must be adjusted to produce 2 to 3 soft stools daily or per PI discretion. Rectal lactulose may be administered in lieu of oral lactulose. Bristol stool type will still be assessed as required by the protocol for subjects dosed with rectal lactulose. Dose amount and frequency for rectal lactulose should be administered according to product label or per PI discretion.
After completion of the blinded randomized treatment phase, defined as OHE resolution, subjects who continue on to the open-label safety follow-up period will receive 30 days of open-label treatment with Xifaxan® 550 mg upon hospital discharge, regardless of the treatment arm in which they were previously randomized. Open-label drug should only be dispensed upon hospital discharge. Please note this may be on a different day than OHE resolution. If subjects remain hospitalized following OHE resolution, standard of

care treatment (which may include Xifaxan® 550 mg) should be given until hospital discharge.

6.0 STUDY MATERIALS

6.1 Description of Treatments

Rifaximin SSD will be supplied as light blue-colored, coated, round, biconvex tablets each containing 40 mg or 80 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.

Two tablet formulations have been formulated with varying concentrations of intragranular CCS: immediate release (IR) with 10% w/w CCS, and sustained extended release (SER) with 0% w/w CCS.

6.2 Description of Comparator Treatments

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.

6.3 Description of Lactulose

Lactulose will be supplied by the hospital and dosed in accordance with label instructions. The adult, oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 to 30 gm of lactulose) TID. The dosage must be adjusted to produce 2 to 3 soft stools daily or per PI discretion. Rectal lactulose may be administered in lieu of oral lactulose. Bristol stool type will still be assessed as required by the protocol for subjects dosed with rectal lactulose. Dose amount and frequency for rectal lactulose should be administered according to product label or per PI discretion. Use of lactulose (dosing time and amount) as well as stool appearance as assessed by the Bristol Stool Chart (Appendix E) will be documented in the eCRF.

6.4 Instructions for Use and Administration

Doses of rifaximin SSD and placebo will be taken orally with water, and tablets will be swallowed whole.

The study drug should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F).

6.5 Packaging and Labeling

The study drug will be packaged and labeled in a manner consistent with the study design.

Each multi-use blister pack of rifaximin SSD 40 mg IR tablets, rifaximin SSD 80 mg SER tablets, and SSD placebo tablets will bear a label that meets applicable laws for an investigational drug, which includes, but is not limited to, the following information:

- Protocol Number
- Kit Number
- Space for entry of the subject's initials
- Space for the entry of date dispensed
- A statement reading: "Caution: New Drug Limited by Federal Law to Investigational Use"
- A statement reading, "Manufactured for Salix Pharmaceuticals, Inc., a wholly-owned subsidiary of Valeant Pharmaceuticals NA LLC"
- A statement indicating the quantity of product contained
- A statement reading, "Keep out of the Reach of Children"
- A statement reading, "Store at controlled room temperature 20 to 25°C (68 to 77°F) with excursions permitted 15 to 30°C (59 to 86°F)"

6.6 Accountability

The Investigator is responsible for ensuring that the designated investigational center staff member will conduct a complete inventory of study materials and assume responsibility for their storage and dispensing. In accordance with federal regulations, the investigators must agree to keep all study materials in a secure location with restricted access. The investigator will keep a record of the inventory and dispensing of all study drug. This record will be made available to the site's monitor for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the investigators will be accounted for and, in no case, used in any unauthorized situation. Upon receipt, all shipment supplies must be acknowledged and documented, stored and/or returned appropriately. Following verification, and as directed by the Sponsor, all used and unused product must be returned to the Sponsor or, with the Sponsor's permission, disposed of at the site in an appropriate manner. The procedure for

documenting and performing drug return or destruction will be provided to the site by the Sponsor designee.

6.7 Methods of Assigning Subjects to Treatment Groups

This is a double-blind study, in which the identity of the study drug will be unknown to both investigator/evaluator and subjects, as well as all individuals closely associated with the study. Subjects will be randomized to 1 of 5 treatment groups in a 1:1:1:1:1 ratio [rifaximin SSD 40 mg IR (QD and BID), rifaximin SSD 80 mg (QD and BID), and placebo BID]. Each screened subject will be assigned a screening number by the investigational center, which will consist of the XX-digit site number (pre-assigned by Sponsor/designee) and the 3-digit chronological order screening number, starting with '001' (e.g., XX-001, XX-002).

The study drug kit will be assigned to the subject based on a randomization code and kits will be dispensed to the subjects by the randomization system at the Day 2 visit.

6.8 Randomization and Blinding

The study drugs will be packaged and labeled identically. In the SSD QD cohorts blinding will be maintained by administering placebo as the second daily dose. Study drug kits will be numbered sequentially and dispensed randomly to the subjects entering the study within each investigational center. Study drug supplies will be distributed to the investigational sites to maintain the randomization ratio within each investigational center.

As a double-blinded study, the investigators, the site staff, the sponsor, and the clinical monitors will not be aware of the treatment assigned to the individual study subjects. Delegated staff members at each investigational center will dispense the study drugs and will collect all used and unused study drug containers as scheduled.

6.9 Unblinding

A few designated members of the Sponsor's team not involved in the ongoing activities of the study will be unblinded as a result of the interim analysis performed when at least 10 subjects per treatment group have completed participation in the blinded treatment period of the study. Otherwise, the treatment assignments for all enrolled subjects will be unblinded only after completion of the 30 day open-label safety follow-up period. Specifically, the blind will be broken only after all subject data are entered and cleaned according to the study Data Management Plan and the study database is locked.

In the case of a medical emergency, the investigator can break the blind for the subject involved preferably by first discussing the situation with the medical monitor and the sponsor (or designee) immediately. After confirmation, the investigator will be contacted with unblinding information by a sponsor representative. The investigator will record the code break in the subject's source documents.

7.0 EFFICACY AND SAFETY ANALYSIS

7.1 Safety and Efficacy Endpoints

Primary Efficacy Endpoints

The primary efficacy variable is the time to OHE resolution as measured by the Hepatic Encephalopathy Grading Instrument (HEGI; Appendix A). Using an iterative Delphi method, Steering Committee and international hepatologist panel, the West Haven Criteria (WHC; Appendix B) scale was modified to develop a clinician tool for OHE identification and grading. Major diagnostic criteria include: disorientation (time, place, and/or person), presence of both lethargy and asterixis, and somnolence coma.

Inter- and intra-rater HEGI reproducibility were 97 % and 98 %, respectively. When applied to a phase II clinical trial population of 178 patients with 388 OHE episodes, HEGI demonstrated excellent concordance with investigator judgment (Bajaj et al, 2016).

The HEGI is used to standardize investigator determination as to whether a patient with a documented history of cirrhosis and HE is experiencing or has experienced an Overt HE episode. The patient is considered to be having an Overt HE episode if at least one of the following applies: 1) Disorientated to time or place or person; 2) Lethargic and has asterixis and/or 3) Inability to assess the patient due to disorientation to time and place and person; and/or somnolence, and/or coma. Clinical findings must have been present for at least 1 hour to be considered an OHE episode. Resolution of OHE must be confirmed with a repeat evaluation using the HEGI at least 3 and no more than 12 hours after the initial evaluation to demonstrate persistence of resolution. NOTE: Subjects should continue to dose on blinded study medication until OHE resolution is confirmed.

Secondary Efficacy Endpoints:

The following secondary efficacy variables will also be assessed:

- Time to OHE resolution defined as a West Haven Criteria (WHC) score of 0 or 1
- Time to 1 unit decrease in WHC score during the randomized treatment period.
- Change from Baseline in WHC score at Day 15 or end of blinded treatment period, whichever occurs first.

- Change from Baseline in HEGI score at Day 15 or end of blinded treatment period, whichever occurs first.
- Time to improvement in HEGI score.
- Length of hospitalization from Baseline to End of Blinded Treatment Phase.

Safety Endpoints:

Safety assessments will include the following:

- Incidence of treatment-emergent adverse events (TEAEs).
- Change from baseline to OHE resolution in vital sign measurements and clinical laboratory values.
- Incidence of infections, such as spontaneous bacterial peritonitis (SBP), urinary tract infection, pneumonia, bacteremia, and cellulitis.

Open-label Safety Follow-up Phase:

- Reoccurrence of OHE during the 30 day follow-up period.
- Readmission to hospital during the 30 day follow-up period.
- Change from Baseline to study exit in indices of Health Outcome using the Caregiver Burden Inventory (CBI; Appendix C)
- Change during Follow-up Phase (from first follow-up visit post OHE resolution to study exit) in Chronic Liver Disease Questionnaire (CLDQ; Appendix D).

7.2 Statistical Hypothesis

The log-rank test is a statistical method for comparing distributions of time until the occurrence of an event of interest among independent groups. The null hypothesis tested by the log-rank test is that of equal time distribution among groups. Rejection of the null hypothesis indicates that the event rates differ among groups at one 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 resolution for each SSD group and the placebo group, respectively.

7.3 Sample Size

Approximately 325 subjects will be randomized in 1:1:1:1:1 ratio to rifaximin SSD tablets [40 mg immediate release (IR)] QD plus lactulose, rifaximin SSD tablets [40 mg immediate release (IR)] BID plus lactulose, rifaximin SSD tablets [80 mg sustained

extended release (SER)] QD plus lactulose, rifaximin SSD tablets [80 mg sustained extended release (SER)] BID plus lactulose and placebo BID plus lactulose.

The sample size estimation is based on cumulative probability distributions of the times from baseline until the first OHE resolution (HEGI score <2) between treatment groups using the log-rank test.

This sample size estimation is based on a previous study with rifaximin (Sharma 2013). It is assumed that approximately 76% of rifaximin plus lactulose subjects and 51% of placebo plus lactulose subjects will experience OHE resolution over the course of up to 14 days of treatment. With two-sided type I error rate of 0.05, approximately 61 evaluable subjects per treatment group will provide at least 80% power to demonstrate the superiority of rifaximin SSD to placebo using the log-rank test.

7.4 Study Populations

Intent to Treat (ITT): The ITT population will include all randomized subjects who received at least one dose of study drug.

Analysis on the ITT sample will be used as the primary efficacy analysis and will be performed for all efficacy endpoints. Subjects will be analyzed in the treatment group to which they were randomized.

Per Protocol (PP): The PP population will include all ITT subjects who remain in the study through the end of the blinded 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.

Safety: The safety population will include all subjects who received at least 1 dose of study drug. All subjects in the safety population will be analyzed according to the treatment they actually received.

7.5 Statistical Analysis

7.5.1 Methods of Analysis

All continuous variables will be summarized using descriptive statistics including the sample size (N), mean, SD, median, minimum, and maximum. All categorical variables will be summarized using frequency counts and percentages.

7.5.2 Subject Disposition

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

7.5.3 Demographics and Baseline Characteristics

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

Baseline characteristics include:

- HEGI grade (Appendix A)
- WHC score (Appendix B)
- Serum ammonia levels
- Comprehensive Metabolic/Liver Panel (including ALT, AST, ALP, DBil, TBil, ProTime, INR; total serum protein)
- Hematology: CBC w/Differential
- Alpha fetoprotein (AFP) only in lieu of recent HCC imaging at screening only
- Serum pregnancy test. NOTE: Serum pregnancy tests performed upon hospital admission, prior to study consent, may be used at Screening.
- Urinalysis
- Current Rifaximin use at screening (Yes vs. No)
- Current lactulose use for maintenance of remission at screening (Yes vs. No) and dosage
- Time since first diagnosis of advanced liver disease, defined as first dose date minus date of first diagnosis of advanced liver disease + 1
  (randomization date will be used if first dose date is missing)
- Time since first diagnosis of hepatic encephalopathy, defined as first dose date minus date of first diagnosis of hepatic encephalopathy + 1
  (randomization date will be used if first dose date is missing)
- Number of HE episodes within the past 6 months
- Factors contributing to HE episodes
- Diabetes at Screening (Yes vs. No)

7.5.4 Efficacy Endpoint Analyses

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the time to OHE resolution as measured by the HEGI, a modified West Haven Criteria scale. OHE resolution is defined as a HEGI grade of < 2. Resolution of OHE must be confirmed with a repeat evaluation using the HEGI at least 3 and no more than 12 hours after the initial evaluation to demonstrate persistence of resolution. Time to resolution of OHE is defined as the duration between the date/time of first dose of study drug (baseline) and the date/time of first documented resolution of OHE via the HEGI. Subjects who complete the 14 day randomized treatment period without experiencing OHE resolution will be censored at 14 days.

The primary efficacy analysis of time to OHE resolution between each active rifaximin SSD plus lactulose treatment group and the placebo plus lactulose group will be tested using the log-rank test.

Analysis of primary efficacy endpoint will be tested in ITT and PP populations.

Analysis of Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints will be based on the ITT population.

- Time to OHE resolution defined as a WHC score of 0 or 1
- Time to 1 unit decrease in WHC score during the randomized treatment period.
- Change from Baseline in WHC score at Day 15 or end of blinded treatment period, whichever occurs first.
- Change from Baseline in HEGI score at Day 15 or at end of blinded treatment period, whichever occurs first.
- Time to improvement in HEGI score.
- Length of hospitalization from Baseline to End of Blinded Treatment Phase.

7.5.5 Safety Endpoints Analyses

All safety analyses will be performed for the Safety Population. Each analysis will consist of a summary of data within each treatment group.

Adverse Events:

Adverse events will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary. Treatment-emergent AEs will be defined as any event with a start date occurring on or after initial treatment (baseline visit) or, if pre-existing, worsening after initial treatment (baseline).

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

Treatment-emergent AEs will be summarized as follows:

- Number and percentage of subjects experiencing TEAEs;
- Number and percentage of TEAEs by relationship to study treatment (i.e. related or unrelated);
- Number and percentage of TEAEs by severity (i.e., mild, moderate or severe);
- Number and percentage of subjects experiencing serious AEs (SAEs);
- Number and percentage of subjects experiencing study drug-related SAEs;
- TEAE leading to permanent treatment discontinuation;
- TEAEs with an outcome of death.

The incidence of treatment-emergent AEs of infections, such as SBP, UTI, pneumonia, bacteremia and cellulitis will be summarized by each treatment group.

If a subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE, using the most severe intensity. Severity and AE leading to early termination will also be presented for these infection AEs.

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

7.5.6 Clinical Laboratory Findings

Laboratory data will be summarized at baseline and at each visit, as well as changes from baseline in laboratory parameters. For each summary the N, mean, median, SD, minimum, and maximum values will be given by treatment group. Pretreatment laboratory values obtained closest in time to first dose of study drug will be used for summarization of baseline and change from baseline. Clinical laboratory tests performed during the study will be analyzed by a local clinical laboratory. To standardize the laboratory reference values the normal laboratory values listed in the Merck Manual will be used.

- Serum ammonia levels
- Comprehensive Metabolic/Liver Panel (including ALT, AST, ALP, AFP, DBil, TBil, ProTime, INR; total serum protein)
- Hematology: CBC w/Differential
- Alpha fetoprotein (AFP) only in lieu of recent HCC imaging at screening only
- Serum pregnancy test. NOTE: Serum pregnancy tests performed upon hospital admission, prior to study consent, may be used at Screening.
- Urinalysis
- Urine pregnancy test

7.5.7 Vital Signs Measurements

Vital signs will be summarized at baseline and at each visit, as well as changes from baseline in vital sign measurements. For each summary the N, mean, median, SD, minimum, and maximum values will be given by treatment group. Pretreatment vital signs obtained closest in time to first dose of study drug will be used for summarization and analysis of baseline and change from baseline vital signs.

Vital signs will include supine blood pressure (mmHg), heart rate (beats per minute), respiratory rate, weight and temperature. Height (cm) will be collected at Screening only.

Vital sign measurements will be collected at every visit. Supine blood pressure measurements should be measured on the same arm throughout the study.

7.6 Interim Analysis

An interim analysis will be conducted when at least 10 subjects per treatment group have completed participation in the blinded treatment period of the study. The CRO/Sponsor designee will remain blinded, whereas a few designated members of the Sponsor's team who do not have direct involvement with the ongoing study will be unblinded at the interim analysis stage. The interim results will not be shared outside of the small designated team, and no changes will be made to the ongoing study based on the interim study results.

8.0 STUDY METHODS

8.1 Study Visits

Following identification of a potential subject, the Investigator (or designee) will explain the purpose of the study, procedures, risks/benefits, and subject responsibilities to the potential subject's caregiver. The subject's ability to meet the requirements of the study will be determined in discussions with the caregiver. If the caregiver consents on behalf

of the subject the person obtaining written consent will sign and date the IRB/EC-approved ICF, at which point the subject is considered part of the study population. The original signed document will be retained in the subject records, and a copy will be provided to the subject/caregiver. In addition, the applicable privacy regulation requirements must be met.

Study Visit procedures are outlined in Table 1.

Table 1: Study Design and Schedule of Assessments

	Blinded Randomized Treatment Period			Open-label Safety Follow-up Period		
GENERAL & SAFETY ASSESSMENTS:	**Screening & Baseline**	**Treatment Period**	**Hospital Discharge**	**Follow-up[4] Visit 1**	**Follow-up[4] Visit 2**	**Follow-up[4] Visit 3/ EOS[8]**
Study Day	**Study Day 1**	**Study Day 2 Up to Study Day 15**		**Day 7 Post Resolution (±2)**	**Day 14 Post Resolution (±2)**	**Day 30 Post Resolution (±2)**
Informed Consent	X					
Review inclusion / exclusion criteria	X					
Medical History and Demographics	X					
Record Concomitant Medications	X	X	X	X	X	X
Discontinue use of prohibited medications	X					
Vital Signs and Weight (kg)	X	X		X	X	X
Height (cm)	X					
Physical Examination	X	X[2]		X	X	X
Clinical Laboratory Tests/ Urinalysis	X[5]	X		X	X	X
Serum/Urine Pregnancy Test	X[6]					X[6]
HEGI[1]	X	X[2]		X	X	X
WHC[1]	X	X[2]		X	X	X
CBI[1]	X			X	X	X
Randomize Subject in EDC	X					
Dispense/Administer 1st Dose of Blinded Study Drug		X[2]				
Record dates/times of study drug dosing		X				
Record Bristol Stool Appearance		X				
Record lactulose use (dosing time and amount) dates/times of lactulose use	X	X		X[3]	X[3]	X[3]
Assess Open-Label Dosing Compliance				X[3]	X[3]	X[3]
Record Adverse Events	X	X	X	X	X	X
Dispense Open Label Xifaxan® 550mg and Review Dosing Instructions			X[7]			
CLDQ[1]				X	X	X

Abbreviations: EOS = end of study

All Subject assessments will be performed by a trained and qualified Evaluator. Efforts should be made to have the same evaluator assess the same Subject for as many HEGI assessments as possible. Every effort must be made for the same Evaluator to conduct the HEGI assessments at both the resolution of OHE and the confirmation of resolution assessed 3 to 12 hours later.

[1]Evaluator, defined by only licensed physicians, physician's assistants or nurse practitioners, who are trained in these instruments may conduct the assessment.

[2]Assessments are conducted twice per day, approximately 12 hours (±2 hours) apart. Following resolution of OHE, a confirmatory HEGI (3 to 12 hours post initial resolution) must be done to complete the blinded randomized treatment phase.. Subjects should continue to dose on blinded study medication until OHE resolution is confirmed.

[3]Subject will report on lactulose use (if any) and open-label dosing compliance from previous visit to current visit. Diary cards are not being used on this study.

[4]Open-label Safety Follow-up visits will be conducted by a study investigator.

[5]Clinical laboratory tests run within 24 hours of consent, may be used in place of drawing new labs at Screening provided all protocol required labs are present. Note: AFP is only required at Screening.

[6] Serum pregnancy test is done at Screening and urine pregnancy test at EOS visit (open-label safety follow-up Visit 3)

[7] Open-label drug should only be dispensed to subjects upon hospital discharge. Please note this may be on a different day than OHE resolution.

[8] If a subject early terminates/discontinues during the study, the visit schedule at the end of the that treatment phase should be followed for their ET visit.

8.1.1 Day 1: Screening / Baseline

The following procedures are to be completed at the Screening/Baseline visit, prior to randomization:

- Informed consent is to be signed by the subject's caregiver prior to performing any study evaluations or procedures, including discontinuing any prohibited medications.
- Allocate subject screening identification number to eligible subjects in ascending order using the next available consecutive number on the list.
- Review Inclusion/Exclusion criteria to ensure subject qualifies for the study.
- Conduct serum pregnancy test (for female subjects of childbearing potential) and confirm that it is negative. Note: Serum pregnancy tests performed upon hospital admission, prior to study consent, may be used at Screening.
- Complete a full physical examination, including evaluation for complications of liver cirrhosis.
- Collect demographic information, significant medical history, and hospital admission data including diagnosis of liver cirrhosis and OHE and HEGI grade.
- Collect vital sign measurements (include weight, height, supine blood pressure, heart rate, respiration rate and temperature). Height will only be collected at Screening.
- Record all concomitant medications administered within the 30 days prior to screening visit, and ensure that all prohibited medications are discontinued
- Collect blood and urine for clinical laboratory tests (hematology, blood chemistry, and urinalysis). Labs drawn within 24 hours of consent may be used at Screening provided all protocol required labs are present.
- Subject must have a Grade 2 or Grade 3 HEGI score (Appendix A) following lactulose treatment and adequate hydration (IV fluids at PI discretion). NOTE: Duration of hospital admission prior to enrollment is not restricted provided the hydration and lactulose treatment occurred within a reasonable timeframe to subject randomization.
- Determine and record WHC score. (Appendix B)
- Assess Caregiver Burden Index (CBI; Appendix C).

After all Screening/Baseline procedures have been completed and necessary information has been collected:

- Randomize subject onto study using a randomization code obtained from the IRT.
- Record date, time(s) and dose(s) of lactulose.
- Record all AEs.

8.1.2 Day 2 up to Day 15: Randomized Treatment Period

The following are to be conducted each day the subject is hospitalized.

Conducted Daily

- Record all concomitant medications and AEs.
- Collect vital sign measurements (include weight, supine blood pressure, heart rate, respiration rate and temperature).
- Collect blood and urine for clinical laboratory tests (hematology, blood chemistry, and urinalysis).
- Dispense study drug and administer dose to subject.
- Record date and times of study drug dose.
- Record date, time(s) and dose(s) of lactulose.
- Record frequency of bowel movements and stool appearance. (Bristol, Appendix E)

Conducted TWICE Daily at 12 Hour (±2 Hr) Intervals (approx. 7AM and 7PM)

- Complete a full physical examination, including evaluation for complications of liver cirrhosis.
- Determine and record HEGI score. (Appendix A)
- Determine and record WHC score. (Appendix B)

Criteria for OHE Resolution

For the purposes of this clinical study, OHE resolution is determined solely on the HEGI score. A HEGI score of < 2 indicates resolution of OHE, whereas a HEGI score of ≥2 indicates a continuation of the OHE episode.

Resolution of the OHE episode (HEGI score of < 2) must be confirmed by a repeat evaluation (HEGI) at least 3 and no more than 12 hours after the initial evaluation to demonstrate persistence of the OHE resolution.

- If the OHE resolution is not confirmed by this repeat evaluation, the subject continues in the study until OHE resolution occurs again and is subsequently confirmed by a repeat evaluation 3-12 hours following.
- If the OHE resolution is confirmed by this repeat evaluation, the subject is considered resolved. Resolution of OHE will be recorded as the date/time of the HEGI assessment immediately prior to the confirmation evaluation. NOTE: Subjects should continue to dose on blinded study medication until OHE resolution is confirmed.

8.1.3 OHE Resolution

The following procedures will occur upon OHE resolution with confirmatory HEGI.

- Record all concomitant medications and AEs.

- Collect vital sign measurements (include weight, supine blood pressure, heart rate, respiration rate, and temperature).
- Complete a full physical examination, including evaluation for complications of liver cirrhosis.
- Collect blood and urine for clinical laboratory tests (hematology, blood chemistry, and urinalysis).
- Determine and record HEGI score. (Appendix A)
- Determine and record WHC score. (Appendix B)
- Dispense Xifaxan® 550mg (BID dosing) and review dosing instructions with subject.
- Schedule and review the open-label safety follow-up visits with subject.
- Record stool appearance. (Bristol, Appendix E)

If the subject discontinues or early terminates from the study prior to starting the open-label safety follow-up period, the OHE Resolution visit assessments are to be done as the subjects early termination/discontinuation visit and the subject exited from study. Please refer to Section 8.3.1 for a list of early termination/discontinuation procedures to be conducted.

8.1.4 Hospital Discharge Visit

The following procedures will occur if the subject is not discharged from the hospital on the same day as OHE resolution:

- Record all concomitant medications and AEs.
- Dispense Xifaxan 550 mg (BID dosing) and review instructions with subject.
- Schedule and review the open-label safety follow-up visits with subject.

8.1.5 Open-label Safety Follow-up / Visit 1 (Day 7 ±2)

Follow-up Visit 1 will occur 7 days (± 2 days) following a confirmed resolution of OHE. Note that OHE resolution and subject discharge may not occur on the same day.

- Record all concomitant medications and AEs.
- Collect vital sign measurements (include weight, supine blood pressure, heart rate, respiration rate and temperature).
- Complete a full physical examination, including evaluation for complications of liver cirrhosis.
- Collect blood and urine for clinical laboratory tests (hematology, blood chemistry, and urinalysis).
- Record date, time(s) and dose(s) of lactulose, if taken.
- Determine and record HEGI score. (Appendix A)
- Determine and record WHC score. (Appendix B)

- Assess health outcomes indices via CBI (Appendix C) and CLDQ (Appendix D).

8.1.6 Open-label Safety Follow-up Visit 2 (Day 14 ±2)

Follow-up Visit 2 will occur 14 days (± 2 days) following a confirmed resolution of OHE. Note that OHE resolution and subject discharge may not occur on the same day.

- Record all concomitant medications and AEs.
- Collect vital sign measurements (include weight, supine blood pressure, heart rate, respiration rate and temperature).
- Complete a full physical examination, including evaluation for complications of liver cirrhosis.
- Collect blood and urine for clinical laboratory tests (hematology, blood chemistry, and urinalysis).
- Record date, time(s) and dose(s) of lactulose, if taken.
- Determine and record HEGI score. (Appendix A)
- Determine and record WHC score. (Appendix B)
- Assess health outcomes indices via CBI (Appendix C) and CLDQ (Appendix D).

8.1.7 Open-label Safety Follow-up / Visit 3 (EOS) (Day 30 ±2)

Visit 3 (EOS) Visit will occur 30 days (± 2 days) following a confirmed resolution of OHE. Note that OHE resolution and subject discharge may not occur on the same day.

- Record all concomitant medications and AEs.
- Collect vital sign measurements (include weight, supine blood pressure, heart rate, respiration rate and temperature).
- Complete a full physical examination, including evaluation for complications of liver cirrhosis.
- Collect blood and urine for clinical laboratory tests (hematology, blood chemistry, and urinalysis).
- Record date, time(s) and dose(s) of lactulose, if taken.
- Determine and record HEGI score. (Appendix A)
- Determine and record WHC score. (Appendix B)
- Assess health outcomes indices via CBI (Appendix C) and CLDQ (Appendix D).
- Conduct urine pregnancy test.

If the subject discontinues or early terminates from the study during the open-label safety follow-up period, the Visit 3 (EOS) visit assessments will be followed as the subject early

termination/discontinuation visit and the subject exited from study. Please refer to Section 8.3.1 for a list of early termination/discontinuation procedures to be conducted.

8.1.8 Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional exams should be fully documented in the source documents and on Unscheduled Visit CRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not Unscheduled Visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit CRF.

If a subject is seen for multiple visits during a given visit timeframe, the data from the visit that is intended to meet the protocol requirements for the scheduled visit, should be captured on the visit CRF. Where such a determination cannot be made, the first visit within the scheduled visit interval will be used for completion of the protocol required scheduled visit CRF. Data from any additional visits within a scheduled visit interval will be captured on an Unscheduled Visit CRF.

8.1.9 Missed Visits

If a subject misses any scheduled follow-up visit and cannot be seen prior to the start of the visit range for the next scheduled follow-up visit, the visit is considered missed.

8.2 Post-Study Follow-up

If a subject requires further follow-up of AEs upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary. Refer to for follow-up of AEs following study exit.

8.3 Study Completion

The Sponsor will notify the Investigator when to contact the IRB to inform them that the study is complete.

8.3.1 Early Study Termination

If the subject discontinues or early terminates from the study during the blinded treatment period, the following assessments are to be collected:

- All concomitant medications and AEs.
- Vital sign measurements (include weight, supine blood pressure, heart rate, respiration rate, and temperature).

- Complete physical examination, including evaluation for complications of liver cirrhosis.
- Blood and urine for clinical laboratory tests (hematology, blood chemistry, and urinalysis).
- HEGI score. (Appendix A)
- WHC score. (Appendix B)

If the subject discontinues or early terminates from the study during the open-label safety follow-up period, the following visit assessments are to be collected:

- All concomitant medications and AEs.
- Vital sign measurements (include weight, supine blood pressure, heart rate, respiration rate and temperature).
- Complete physical examination, including evaluation for complications of liver cirrhosis.
- Blood and urine for clinical laboratory tests (hematology, blood chemistry, and urinalysis).
- Record date, time(s) and dose(s) of lactulose, if taken.
- HEGI score. (Appendix A)
- WHC score. (Appendix B)
- Assess health outcomes indices via CBI (Appendix C) and CLDQ (Appendix D).
- Urine pregnancy test.

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the Investigators, IRB, and FDA, as applicable. The Sponsor will instruct the Investigators to stop dispensing study materials/treatment and to arrange for study closeout at each site.

8.4 Concomitant Medications/Therapy

All concomitant medications administered within 30 days of Day 1 (Screening/Baseline) will be recorded in the subject's medical records and case report form (CRF).

Permitted Therapy

1. Direct-acting antivirals and hepatitis B virus suppression therapy permitted following AASLD guidelines.

2. Stable dose of antidepressants and/or benzodiazepines if the dose and regimen are expected to remain unchanged throughout the trial.
3. Prescription and non-prescription sleep aids [e.g., Lunesta™ (eszopiclone) and Intermezzo® or Ambien® (zolpidem tartrate)].
4. Stable dose of Neurontin (gabapentin) and Lyrica (pregabalin) if the dose and regimen are expected to remain unchanged throughout the trial.
5. Diuretics (including diuretics for the management of ascites).

Prohibited Therapy

Any prohibited medications used during the study will be recorded on the concomitant medication page of the CRF.

1. Non-study rifaximin (e.g., commercial rifaximin, Xifaxan® 550 mg tablets), Rifampin or other rifamycin derivatives are prohibited upon subject consent to the study.

   Note: After completion of the blinded randomized treatment phase, defined as OHE resolution, subjects will who continue on to the open-label safety follow-up period will receive 30 days of open-label treatment with Xifaxan® 550 mg upon hospital discharge, regardless of the treatment arm in which they were previously randomized. Open-label drug should only be dispensed upon hospital discharge. Please note this may be on a different day than OHE resolution.

   If subjects remain hospitalized following OHE resolution, standard of care treatment (which may include Xifaxan® 550 mg) should be given until hospital discharge,, at which time the subjects will receive 30 days of open-label Xifaxan® 550 mg.

The following concomitant medications are prohibited within 30 days of Day 1 (Screening/Baseline) and throughout the study:

1. Milk thistle.
2. Investigational drug product or device used within 30 days or 5 drug half-lives (whichever is longer) prior to Baseline.
3. P-glycoprotein inhibitors: including but 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.

The following concomitant medications are prohibited after Day 1 (Screening/Baseline) through the EOS visit:

1. P-glycoprotein inhibitors.
2. Coumadin (warfarin) or coumarin derivatives.

3. Alternative, natural, herbal, and/or dietary supplements that may affect the course of the liver disease (including but not limited to: Milk Thistle, St John's Wort, Echinacea, etc.).

8.5 Treatment Compliance

Any subject, who does not follow instructions to a degree that, in the Sponsor or Investigator's opinion, jeopardizes the subject's well-being, may be discontinued.

8.6 Protocol Deviations

The date of and reason for deviations, will be documented for all cases. Significant or major protocol deviations impacting the safety of the subject or the integrity of the study must be reported by the Investigator to the IRB/EC immediately. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB/EC.

Protocol assessments will continue until the end of the study, unless the protocol deviations put the subject at risk or the subject's condition requires that he/she be discontinued from the study.

9.0 ADVERSE EVENTS

Salix maintains a robust pharmacovigilance system comprised of a governance framework and standard operating procedures supporting a systematic process for review, evaluation, and management of accumulating safety data from clinical trials and other sources to:

- Identify a potential new safety signal.
- Ensure that an investigational product's risks are adequately assessed and communicated to investigators, IRBs/IECs, and regulatory bodies during clinical development.

For this study, safety monitoring activities will include but are not limited to:

- Review and evaluation of single SAE occurrences in real-time as reported through the SAE reporting process as outlined in this section of the protocol;
- Review and evaluation, in real-time, of 1 or more occurrences of an uncommon SAE that is not commonly associated with product exposure;
- Findings and/or safety data obtained during this study will provide information for the overall review of safety that is conducted by Salix on a routine basis. Salix will report expeditiously any findings from clinical trials (ongoing or completed), epidemiological studies, pooled analysis of multiple studies, and

findings from animal or in vitro testing that suggest a significant risk in humans exposed to the study product.

Safety data collection for this study begins at the time of the subject'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 unanticipated problem (refer to Protocol Section 8.1), AE or SAE.

9.1 Operating Definitions for Assessing Safety

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a study product and which does not necessarily have a causal relationship with the 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.

  NOTE: if the pre-existing illness is the disease under study, then "exacerbation" refers to an unexpected worsening from the condition at baseline.
- 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.
- Symptom associated with disease not previously reported by the subject.

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).

- Overdose of either study product or concurrent medication without any signs or symptoms.
- Symptoms associated with disease, which are consistent with the subject's usual clinical course; unless the subject experiences worsening of their symptom(s) or the symptom(s) meet the criteria for an SAE.

9.1.2 Serious Adverse Event

A SAE is any AE, occurring at any dose, which results in any of the following outcomes ("Occurring at any dose" does not imply that the subject received study product):

- Results in death
- Is life threatening

NOTE: Life-threatening means that the subject was, in the view of the investigator or sponsor, at immediate risk of death at the time of the event. This definition 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. "In-patient" hospitalization means the subject has been formally admitted to a hospital for medical reasons for more than 24 hours. It does not include presentation at a casualty or emergency room.

- 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.

- A congenital anomaly or birth defect in the offspring of a subject who received study product.
- Important medical events that do not result in death, are not life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate

medical judgment, they may jeopardize the subject and 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 AE 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 a 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 used in deciding whether prompt reporting is appropriate in case of events that do not meet the serious criteria above.

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

Abnormal laboratory findings (e.g., clinical chemistry, vital signs, hematology) or other abnormal assessments (e.g., abnormal findings during examinations) 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 is clinically significant.

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

At each assessment, after the subject (or caregiver) has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the following standard 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?"

9.3.1 Time Period for Detecting and Reporting of AEs and SAEs

From the time of informed consent through study completion/early termination, including the 30-day open-label safety follow-up period.

9.3.2 Post-Study SAEs

If at any time after 30 days post last study dose, the investigator becomes aware of an SAE which he/she feels is related to study drug or procedure, this must also be reported immediately (within 24 hours of knowledge of occurrence) by telephone and confirmed facsimile transmission/email to CRO/Sponsor designee.

9.4 Documenting AEs and SAEs

All AEs that occur after the subject has signed the ICF and during the course of the study, regardless of causality or seriousness, will be assessed and recorded in the subject's medical records and in the CRF. In addition, SAEs must be documented on the paper SAE Report Form. Should the investigator become aware of an SAE (regardless of its relationship to study drug) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol.

A separate paper SAE Report Form should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same 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 and SAE and not the individual signs/symptoms.

For clinically significant abnormal laboratory findings or other abnormal assessments (such as vital signs) meeting the definition of an AE or SAE, a diagnosis, if known (or clinical signs and symptoms if 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 as an SAE on the SAE Report Form, relevant laboratory data should either be recorded in the 'Details of Relevant Assesments' section of the SAE Report Form (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 SAE Report Form should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to Sponsor designee. It is very important that the investigator provide his/her assessment of causality to study product.

9.5 Severity of Adverse Events

The investigator is to classify the severity of an AE according to the following definitions:

- Mild: Awareness of a sign or symptom but is easily tolerated, requires no treatment and does not interfere with subject's daily activities.
- Moderate: Low level of concern to the subject and may interfere with daily activities, but can be relieved by simple therapeutic care.
- Severe: Interrupts the subject's daily activity and requires systemic therapy or other treatment.

9.6 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/SAE causality:

- Related: There is at least a reasonable possibility that the AE/SAE 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/SAE 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.

9.7 Follow-up of AEs and SAEs

All AEs, regardless of seriousness, must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator is responsible to ensure 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.

CRO/Sponsor designee may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, CRO/Sponsor

designee should be provided with a copy of any postmortem findings, including histopathology.

For SAEs, new or updated information (follow-up information) should be recorded on a new SAE Report Form and the corresponding follow-up number entered must be entered on the form. By signing the SAE Report 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/IEC must be notified about SAEs in accordance with the requirements of the governing IRB/IEC.

9.8 Prompt Reporting of SAEs to CRO/Sponsor Designee

SAEs must be reported promptly to CRO/Sponsor designee once the investigator determines that the event meets the protocol definition of a SAE.

Prompt reporting of a SAE requires:

- Completion and transmission of the SAE Report Form to CRO/Sponsor designee via email/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 CRF within 48 hours of submitting the paper SAE Report Form.
- Prompt reporting of additional information for previously reported 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.

9.9 Pregnancy Reporting

Pregnancies detected in subjects assigned to study treatment should be reported to CRO/Sponsor designee via email/fax within 24 hours of the investigator's awareness, using the Salix Pregnancy Report Form.

If a female subject becomes pregnant following assignment to study treatment, the study product will be immediately discontinued and the subject will be followed until the outcome of the pregnancy is known. (Refer to the 'Females of Reproductive Potential' section).

CRO/Sponsor designee should be notified via email/fax of any updates on the status of the pregnancy within 24 hours of the information becoming available by updating and/or amending the initial pregnancy report form. If a pregnancy is associated with an SAE, an

SAE Report form along with the Salix Pregnancy form should be completed and reported to CRO/Sponsor designee.

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, for medical reasons, will be recorded as an AE or SAE and followed as such.

9.10 Transmission of SAE Report Forms and Pregnancy Report Forms

Completed SAE Report Forms and completed pregnancy report forms should be transmitted to Sponsor designee via the email/fax number provided below:

9.11 Regulatory Reporting Requirements for SAEs

The investigator, or responsible person per local requirements, must comply with the applicable local regulatory requirements related to the reporting of SAEs and IND safety reports to regulatory authorities and their IRB/IEC.

10.0 DATA QUALITY ASSURANCE

10.1 Study Monitoring

The Sponsor's representatives must be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by the Sponsor.

Prior to the start of the study, the Sponsor (or designees) will review the protocol, CRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary during the course of the investigation to verify the following:

- the rights and well-being of subjects are protected
- the conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB/EC requirements
- the integrity of the data, including adequate study documentation
- the facilities remain acceptable
- the Investigator and site personnel remains qualified and able to conduct the study
- test article accountability

During the course of the study, if the Sponsor determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor will take action to secure compliance. In addition, the Sponsor may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the Sponsor's actions.

10.2 Source Documentation

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

Examples of source documents include; hospital records, clinical and office charts, laboratory notes, memoranda, signed ICFs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical investigation. Source documentation worksheets may be provided by the Sponsor to record pertinent information. Source data may also include information initially recorded in an electronic format.

Specific to this study, the eCRF is acceptable as a source document for the following variables and information can be recorded directly onto the eCRF by site personnel:

- subject weight and height
- physical examination
- respiratory rate
- blood pressure
- pulse rate
- body temperature

- time of dosing
- real time of each examination

Subject and/or caregiver completed forms are also considered source data. Only subjects and caregivers are to record information in questionaires. In no instance, should an Investigator or study site personnel record any data or make changes to subject completed forms. The Investigator or designee should review subject/caregiver completed forms. If an entry is found to be illegible or a mistake is found the subject should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, and dating and initialing the change.

Case Report Forms and Data Verification

Subject data required by this protocol are to be recorded on eCRFs. The Investigator and his/her study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification and initials, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. The eCRFs will be submitted to the Sponsor for quality assurance review, data entry, and statistical analysis.

A copy of the eCRFs will be retained by the Investigator, who must ensure that it is stored in a secure place.

10.3 Recording of Data and Retention of Documents

Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator must retain essential documents (indefinitely or specify time, if required) after the completion of the study, unless otherwise notified by the Sponsor. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include but are not limited to the following:

- IRB/EC approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB/EC annual study review
- IRB/EC correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)
- regulatory documents (e.g., financial disclosure and delegation of authority forms)
- all source documents
- eCRFs
- subject's signed ICF
- accountability records for the test article(s)
- correspondence from and to the Sponsor
- any other documents relevant to the conduct of the study

In the event that the Investigator withdraws from the study (e.g., retirement, relocation), study records will be transferred to a mutually agreed upon designee (e.g., another Investigator, site IRB/EC). The Investigator will provide notice of such transfer in writing to the Sponsor.

10.4 Auditing Procedures

Audits of clinical research activities in accordance with the Sponsor's internal Standard Operating Procedures (SOPs) to evaluate compliance with the principles of GCP may take place. A regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority and/or IRB/EC, the Investigator must inform the Sponsor immediately that this request has been made.

10.5 Institutional Review Board/Ethics Committee Approval

The Investigator should ensure that his/her participation in the study, in addition to the protocol, subject recruitment materials (written information or materials including web pages, radio advertisements, television spots or written text developed to encourage subject enrollment) and the ICF to be used in this study are approved by their institution IRB/EC, or if not using their institution's IRB/EC, approved by the reviewing central IRB/EC prior to entering any subjects in the study. Documentation of IRB/EC approval of the study protocol and informed consent must be provided to the Sponsor prior to initiation of the study. In addition, the Investigator must ensure that the reviewing IRB/EC has provided approval for any protocol amendments prior to implementation.

If the amendment necessitates a revision to the ICF, the Investigator should ensure the revised form is also submitted to and approved by the Sponsor and the IRB/EC prior to implementation.

10.6 Publication of Results

All study data generated as a result of this study will be regarded as confidential, until appropriate analysis and review by the Sponsor or its designee and the Investigator(s) are completed. The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with the Sponsor, and such that confidential or proprietary information is not disclosed.

Prior to publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee, for comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Salix Pharmaceuticals, Inc. products and activities receive fair, accurate, and reasonable presentation.

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