CLINICAL TRIAL PROTOCOL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Emricasan, an Oral Caspase Inhibitor, in Subjects with Non-Alcoholic Steatohepatitis (NASH) Cirrhosis and Severe Portal Hypertension

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1 STUDY SYNOPSIS

Protocol

IDN-6556-14

Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Emricasan, an Oral Caspase Inhibitor, in Subjects with Non-Alcoholic Steatohepatitis (NASH) Cirrhosis and Severe Portal Hypertension

Phase of Trial

Phase 2

Objectives

Primary Objective

- To assess whether emricasan compared to placebo leads to a mean decrease in hepatic venous pressure gradient (HVPG) at Week 24 in subjects with NASH cirrhosis and severe portal hypertension

Secondary Objectives

- To assess the safety and tolerability of emricasan
- To characterize the dose response of emricasan on portal pressure as assessed by HVPG at Week 24
- To assess whether emricasan compared to placebo improves HVPG response at Week 24 using a 20% reduction from baseline response definition
- To assess whether emricasan compared to placebo decreases mechanism specific (caspase 3/7) and non-specific alanine aminotransferase (ALT) biomarkers at Weeks 24 and 48

Exploratory Objectives

- To assess whether emricasan compared to placebo improves HVPG response at Week 24 using a 10% reduction from baseline response definition
- To assess whether emricasan compared to placebo improves liver function and prognosis at Weeks 24 and 48 as assessed by model for end-stage liver disease [1] and Child-Pugh (CP) scores (change in score, progression, regression)
- To assess whether emricasan compared to placebo improves biochemical and functional biomarkers (cCK18/M30, flCK18/M65, aspartate aminotransferase [AST], total bilirubin, international normalized ratio [INR], and albumin) at Weeks 24 and 48
- To assess whether emricasan compared to placebo improves fibrosis markers at Weeks 24 and 48
- To assess whether emricasan compared to placebo improves health-related quality of life at Weeks 24 and 48

- To assess whether emricasan compared to placebo decreases development of decompensation or worsening of decompensation at Weeks 24 and 48
- To assess whether emricasan compared to placebo improves liver metabolic function at Weeks 24 and 48 as assessed by methacetin breath test (at select sites)
- To assess whether emricasan compared to placebo improves liver stiffness at Weeks 24 and 48 as assessed by transient elastography (FibroScan®) (at select sites)

Centers

Multicenter, approximately 90 sites in North America and Europe

Number of Subjects

Approximately 240 subjects (60 subjects/arm) will be randomized in a 1:1:1:1 ratio to emricasan 50 mg BID, emricasan 25 mg BID, emricasan 5 mg BID, or matching placebo BID.

Design

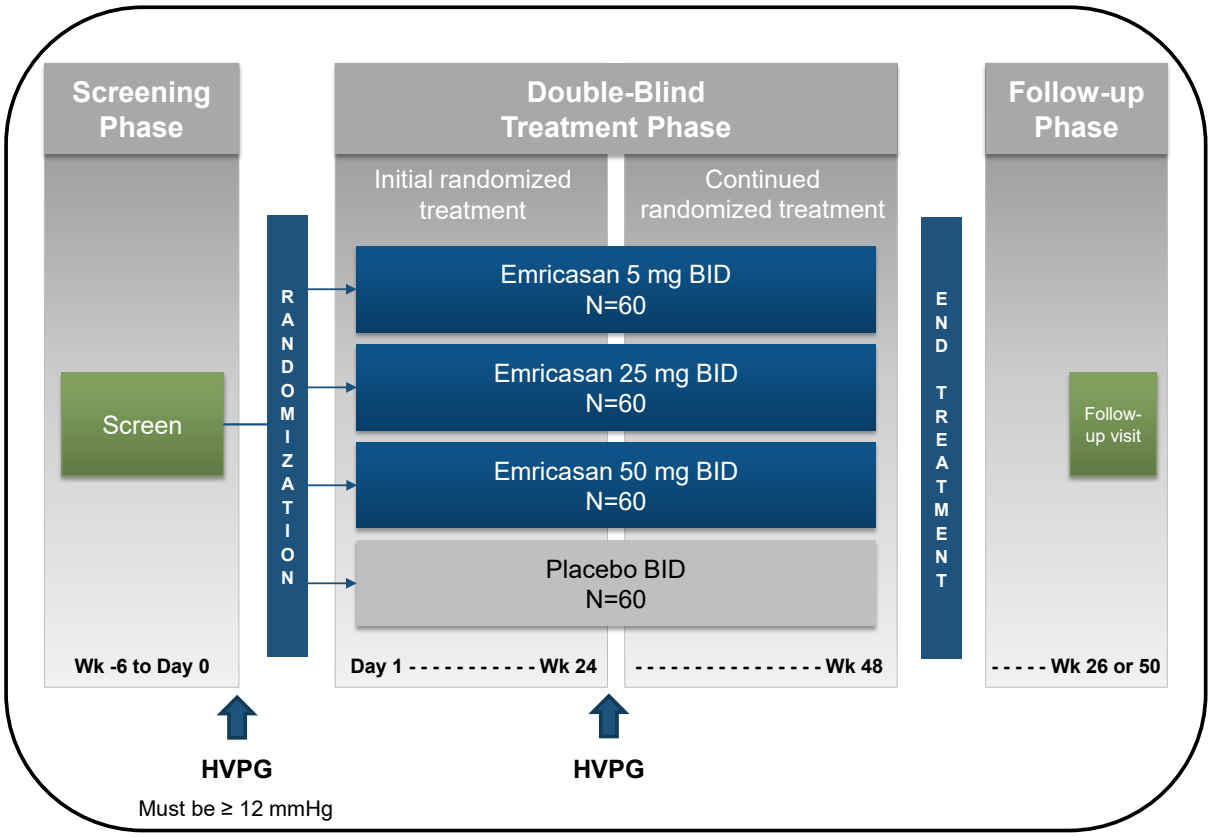
This is a multicenter, double-blind, randomized, placebo-controlled, dose-response study to evaluate the safety and efficacy of emricasan in improving portal hypertension in subjects with NASH cirrhosis and severe portal hypertension (defined as HVPG ≥12 mmHg). Subjects can have compensated (at least 60% of subjects but no more than 75%) or decompensated cirrhosis with no more than 1 prior significant decompensating event and must be currently clinically stable on stable standard therapy [2] (see Inclusion/Exclusion Criteria). Randomization will be stratified by compensated vs. decompensated status at baseline as well as use of non-selective beta-blockers (NSBB) or not. Subjects who are otherwise eligible will undergo the HVPG procedure as the last qualifying procedure prior to Day 1.

The study treatment duration will be up to 48 weeks, including an initial 24-week randomized treatment phase with follow-up HVPG at Week 24 (primary endpoint) and an additional 24-week treatment phase (continuing the same study drug treatment as initially randomized). Subjects completing the initial 24-week randomized treatment phase will be re-consented for the additional 24-week treatment phase. HVPG measurements will be performed at screening and Week 24, with additional placebo-controlled safety follow-up and exploratory efficacy assessments through Week 48. Subjects will complete a final follow-up visit approximately 2 weeks after the end of treatment (i.e., at Week 26 if completing the initial 24-week randomized treatment only or at Week 50 if completing the 48-week treatment).

Subjects with baseline HVPG ≥12 mmHg may experience progression of cirrhosis during the 48-week study. Given that the primary endpoint for this study is HVPG rather than a clinical event (or clinical composite), subjects who have a decompensating event or worsened decompensation during the study will not be required to withdraw and can remain in the study unless the investigator feels the subject is too unstable or the subject requires a transjugular intrahepatic portal shunt or other portosystemic bypass procedure, which would confound the HVPG assessment. Subjects who progress to Child-Pugh C will be withdrawn from study drug but are expected to remain in the study and complete all planned study visits (see Section 8.1.7). All subjects who wish to discontinue study drug treatment should remain in the study and complete all planned study visits, in order to minimize missing data and protect the integrity of the study results. Subjects who withdraw consent for participating in the study

should discontinue study visits. Subjects for whom the investigator deems that it is not in the best interest of the subject to continue participating in the study may also discontinue study visits.

Schema



Dosage and Administration

Study drug will be double-blind with matching placebo. Emricasan at 50 mg, 25 mg, or 5 mg or matching placebo will be administered orally twice a day.

Drug Supply

Emricasan (IDN-6556) and matching placebo will be supplied in bottles containing 60 capsules.

Subject Entry Criteria

Inclusion Criteria

1. Male or female subjects 18 years or older, able to provide written informed consent and able to understand and willing to comply with the requirements of the study.
2. Cirrhosis due to NASH with exclusion of other causes of cirrhosis (e.g. chronic viral hepatitis, alcoholic liver disease, etc.)

- Diagnosis of cirrhosis is based on:
  - Biopsy OR
  - Clinical evidence: platelet count <150,000, AST > ALT, and either nodular liver surface on imaging or splenomegaly
- NASH is based on at least 1 of the following:
  - Prior or current biopsy showing steatohepatitis (fat, ballooning degeneration, inflammation) consistent with NASH
  - At least 2 metabolic risk factors for at least 5 years preceding the diagnosis of cirrhosis: diabetes mellitus, impaired fasting glucose, obesity (BMI ≥30 kg/m^2 or central obesity), hypertension, dyslipidemia (see Appendix IV)
  - Prior or current biopsy showing some but not all diagnostic features of NASH (e.g. only fat or ballooning degeneration or inflammation) but with no evidence for viral hepatitis or other liver disease AND either fatty liver disease on prior imaging or at least 1 metabolic risk factor (as above) for at least 5 years preceding the diagnosis of cirrhosis

    Note: Previous viral hepatitis that was curatively treated (with sustained viral response) is not an exclusion as long as: 1) viral eradication was achieved at least 3 years prior to the diagnosis of cirrhosis and 2) all other criteria are met for NASH as the etiology of cirrhosis

3. Compensated cirrhosis (no history of or presence of clinically evident ascites, variceal hemorrhage, or encephalopathy, and on no medications to treat these complications)

   OR

   Decompensated cirrhosis with no more than 1 prior significant decompensating event:
   a. If prior decompensating event was variceal hemorrhage, event must have occurred at least 3 months prior to Day 1
   b. If prior decompensating event was ascites requiring chronic diuretics, ascites should be well controlled (not clinically evident, i.e. no ascites or ascites only detectable by ultrasound examination) on a stable dose of diuretics for at least 3 months prior to Day 1
   c. If prior decompensating event was hepatic encephalopathy ≥ grade II or requiring hospitalization, encephalopathy should be well-controlled (Stage 0 or 1) on stable medication for at least 3 months prior to Day 1

   Note: Previous transient ascites or hepatic encephalopathy in a subject who is currently stable without clinically evident ascites or encephalopathy and on no medications for these conditions does not count as a prior significant decompensating event
4. Severe portal hypertension defined as HVPG ≥12 mmHg (see Section 8.4.1 for recommendations to identify subjects more likely to meet the HVPG criteria)
5. Subjects who are on NSBB, nitrates, diuretics, lactulose, rifaximin, or statins must be on a stable dose for at least 3 months prior to Day 1
6. Willingness to utilize effective contraception (for both males and females of reproductive potential) from Screening to 4 weeks after the last dose of study drug
7. Platelet count ≤125 k/mm^3 or transient elastography ≥20 kilopascal [3] during screening

8. If on therapeutic dose of vitamin E, stable for 6 months prior to Day 1

Exclusion Criteria

1. Evidence of severe decompensation, defined as:
   a. Presence or history of more than one type of significant decompensating event (clinically evident ascites requiring chronic diuretics, variceal hemorrhage, and/or overt encephalopathy)

   Note: Previous transient ascites or hepatic encephalopathy in a subject who is currently stable without clinically evident ascites or encephalopathy and on no medications for these conditions does not count towards this exclusion (see Inclusion Criteria #4).

   b. One type of decompensating event with the following characteristics:
      - More than 1 episode of variceal hemorrhage or bleeding from a portal hypertensive source (e.g. portal hypertensive gastropathy)
      - Ascites that has required more than 1 large-volume paracentesis (>5 L) for treatment or that has been complicated by spontaneous bacterial peritonitis, hyponatremia (serum Na <130), and/or hepatorenal syndrome
      - More than 1 episode of overt hepatic encephalopathy requiring hospitalization
2. Severe hepatic impairment defined as a Child-Pugh score ≥10
3. ALT >3 times upper limit of normal (ULN) or AST >5 times ULN during screening
4. Estimated creatinine clearance <30 mL/min
5. Prior transjugular intrahepatic portosystemic shunt or other porto-systemic bypass procedure
6. Known portal vein thrombosis
7. Symptoms of biliary colic, e.g., due to symptomatic gallstones, within the last 6 months, unless resolved following cholecystectomy, other definitive treatment (e.g., sphincterotomy), or medical management (e.g., ursodeoxycholic acid)
8. Current use of medications that are considered inhibitors of OATP1B1 and OATP1B3 transporters: atazanavir, cyclosporine, eltrombopag, gemfibrozil, indinavir, lopinavir, ritonavir, rifampin, saquinavir, simeprevir, telaprevir, tipranovir, or some combination of these medications
9. Alpha-fetoprotein >50 ng/mL
10. History or presence of clinically concerning cardiac arrhythmias, or prolongation of screening (pre-treatment) QT Interval Corrected by the Fridericia Correction Formula [QTcF] interval of >500 msec
11. History of or active malignancies, other than those successfully treated with curative intent and believed to be cured
12. Significant systemic or major illness other than liver disease that in the opinion of the investigator would preclude the subject from participating in and completing the study, including but not limited to acute coronary syndrome or stroke within 6 months of screening or major surgery within 3 months of screening
13. Prior liver transplant

14. Change in diabetes medications within 3 months of screening, including initiation, discontinuation, or change in dose except for medications titrated according to blood glucose
15. Uncontrolled diabetes mellitus (HbA1c >9%) within 3 months of screening
16. Restrictive bariatric surgery or bariatric device within 1 year of screening or prior malabsorptive bariatric surgery
17. Known human immunodeficiency virus infection
18. Use of controlled substances (including inhaled or injected drugs) or non-prescribed use of prescription drugs within 1 year of screening to the point of interfering with the subject's ability to comply with study procedures and study drug administration in the investigator's judgement
19. History of significant alcohol consumption (>20 g/day for females and >30 g/day for males on average) within the past 5 years
20. If female: planned or known pregnancy, positive urine or serum pregnancy test, or lactating/breastfeeding
21. Previous treatment with emricasan or active investigational medication (except methacetin) in a clinical trial within 3 months prior to Day 1

Criteria for Evaluation

Safety Variables

- Adverse events
- Vital signs, physical examination
- Laboratory tests (e.g. chemistry, hematology, coagulation, urinalysis)
- ECGs
- Liver and gallbladder events and ultrasound

Efficacy Variables

Primary

- HVPG mean change from baseline at Week 24

Secondary

- HVPG response (20% reduction from baseline) at Week 24
- Caspase 3/7 and ALT at Weeks 24 and 48

Exploratory

- HVPG response (10% reduction from baseline) at Week 24
- MELD and Child-Pugh scores, regression, and progression at Weeks 24 and 48
- cCK18/M30, flCK18/M65, AST, total bilirubin, INR, and albumin at Weeks 24 and 48
- Fibrosis markers at Weeks 24 and 48

- Health-related quality of life, as measured by Short Form-36 (SF-36) and Chronic Liver Disease Questionnaire (CLDQ), at Weeks 24 and 48
- Clinical outcomes (development of decompensation or worsening of decompensation) at Weeks 24 and 48
- Liver metabolic function assessed by methacetin breath test (at select sites) at Weeks 24 and 48
- Liver stiffness by transient elastography (at select sites) at Weeks 24 and 48

Statistical Methods

All efficacy analyses will be based on the Full Analysis Set (FAS) and Per Protocol Set. All safety analyses will be based on the Safety Analysis Set.

The primary endpoint for this study is the change from baseline at Week 24 in HVPG. The change from baseline will be calculated as HVPG at Week 24 minus HVPG at baseline ($HVPG_{W24}$-$HVPG_{BL}$). Comparisons of the mean change from baseline in HVPG at Week 24 between each emricasan treatment group and placebo will be analyzed using a fixed effects Analysis of Covariance (ANCOVA) model using the FAS. This model will include the treatment group, compensated vs. decompensated status, and NSBB use as fixed effects with baseline HVPG as a covariate. Least-square adjusted means (LSMeans) will be reported, along with the estimated difference in LSMeans and corresponding 95% confidence intervals. A Dunnett's test will be applied to adjust for the multiple comparisons of each emricasan treatment group with placebo.

Secondary endpoints include the change from baseline at Weeks 24 and 48 in Caspase 3/7 and ALT measurements and 20% HVPG response at Week 24. Exploratory endpoints include 10% HVPG response at Week 24, change from baseline in MELD and Child-Pugh scores at Weeks 24 and 48, regression/progression in MELD and Child-Pugh scores at Weeks 24 and 48, biochemical and functional biomarkers at Weeks 24 and 48, fibrosis markers at Weeks 24 and 48, quality of life at Weeks 24 and 48, clinical outcome events at Weeks 24 and 48, liver function at Weeks 24 and 48, and liver stiffness measurements at Weeks 24 and 48.

Safety endpoints include treatment compliance, exposure, adverse events, gallbladder adverse effects and ultrasound, potential drug-induced liver injury, additional laboratory parameters, vital signs, and electrocardiogram measurements.

2 LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BID	bis in die, twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
cCK18	Caspase-cleaved cytokeratin 18
CFB	Change from baseline
CFR	Code of Federal Regulations
CI	Confidence interval
CLDQ	Chronic Liver Disease Questionnaire
cm	centimeter
CP	Child-Pugh
CRF	Case report form
CSPH	Clinically significant portal hypertension
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EGD	Esophagogastroduodenoscopy
ELF	Enhanced liver fibrosis
EU	European Union
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FHVP	Free hepatic vein pressure
flCK18	Full-length cytokeratin 18
FSH	Follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good manufacturing practice

HA	Hyaluronic Acid
HbA1c	Glycated Hemoglobin
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HE	Hepatic Encephalopathy
HVPG	Hepatic venous pressure gradient
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IQR	Inter-quartile
ITT	Intention to treat
IVC	Inferior vena cava
IWRS	Interactive Web Randomization System
kg	Kilogram
kPa	Kilopascal
L	Liter
LDL	Low density lipoprotein
LOX-L2	Lysyl oxidase-like 2
LSMeans	Least-square adjusted means
MBT	Methacetin breath test
MCS™	Molecular Correlation Spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for end stage liver disease
mg	Milligram
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
msec(s)	Millisecond(s)

NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
ng	Nanogram
NSBB	Non-selective beta-blocker
OATP	Organic anion transporting polypeptide
P3NP	Aminoterminal propeptide of type III collagen
PK	Pharmacokinetic
PPS	Per Protocol Set
PT	Prothrombin time
QOL	Quality of life
QTcF	QT Interval Corrected by the Fridericia Correction Formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SF-36	Short Form 36
SUSAR	Suspected unexpected serious adverse reaction
TIMP-1	Tissue inhibitor of matrix metalloproteinase 1
ULN	Upper limit of normal
WBC	White blood cell (count)
WHVP	Wedged hepatic vein pressure
YLD	Years lived with disability

3 ETHICS

The study will be conducted in accordance with standards that meet regulations relating to Good Clinical Practice (GCP). These include the European Union (EU) Clinical Trials Directive (2005/28/EC and subsequent amendments and EU Regulation No. 536/2014), International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6, 21CFR Part 312, and applicable regulatory requirements.

The ethical requirements of Institutional Review Boards/Independent Ethics Committees (IRB/IECs) and the Informed Consent Forms (ICFs) are discussed in Section 14, Administrative Aspects.

4 INTRODUCTION

4.1 BACKGROUND

Cirrhosis and Portal Hypertension

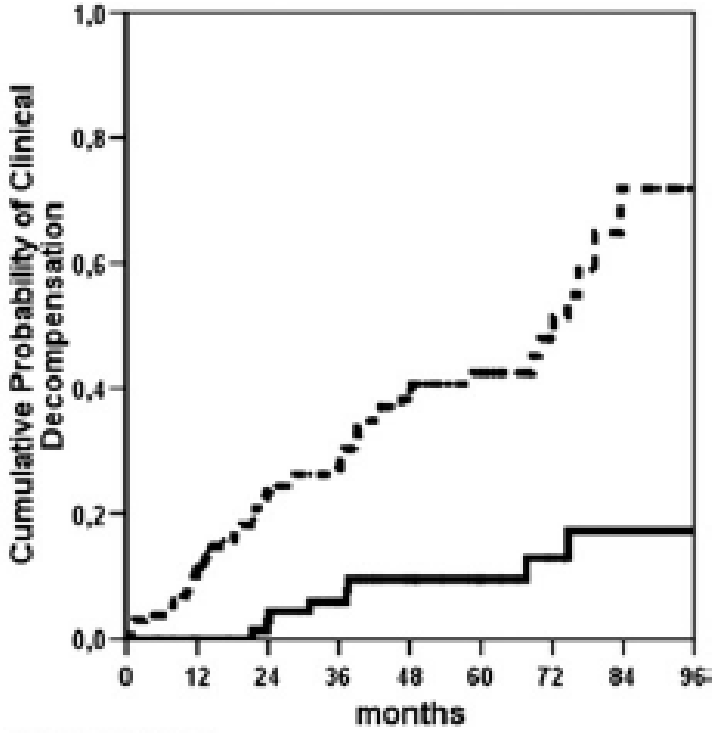
Cirrhosis with portal hypertension is a major public health concern. In 2010, cirrhosis was the 12th leading cause of mortality world-wide, responsible for approximately 1 million deaths [4].This estimate was substantiated by the Global Burden of Disease Study 2013, which estimated that there were ~1.2 million deaths from cirrhosis in 2013 [5] with an overall age-standardized death rate of 18.8/100,000, a rate that is similar in magnitude to all other digestive diseases combined (19/100,000), diabetes mellitus (21.6/100,000) and to neoplasms such as colorectal cancer (12.8/100,000) and stomach cancer (13.8/100,000). Interestingly, cirrhosis predisposes to and is felt to be largely responsible for the development of hepatocellular carcinoma. If deaths due to hepatocellular carcinoma from hepatitis B (300,000), hepatitis C (342,500) and alcohol use (92,000) were included in the cirrhosis death estimates, the number of deaths would almost double. Thus, cirrhosis and portal hypertension are major concerns for public health as well as for patients with those diseases.

Cirrhosis has an important effect upon morbidity and disability. The Global Burden of Disease Study 2013 [6] estimated the years lived with disability (YLD) for 301 acute and chronic diseases between 1990-2013 since that is an important input into global and national health policies. Not surprisingly given the high mortality associated with cirrhosis, cirrhosis was an important and large contributor to YLDs in 2013, with approximately 3.3 million prevalent cases contributing to 545,000 YLDs in 2013.

Once a patient with chronic liver disease progresses to cirrhosis and portal hypertension develops (defined as a hepatic venous pressure gradient [HVPG] >5 mmHg), survival decreases significantly. Cirrhosis consists of at least 2 distinct prognostic stages: compensated and decompensated with the development of clinically overt ascites, variceal hemorrhage, and/or encephalopathy defining the decompensated stage [7]. When a patient with cirrhosis transitions from being “compensated” to “decompensated,” survival is markedly decreased. While patients with compensated cirrhosis have a median survival time >12 years, the median survival time for patients with decompensated cirrhosis is <2 years [7-9].

Portal hypertension is defined as clinically significant portal hypertension (CSPH) once the HVPG is ≥10 mmHg. In a study of 213 patients with compensated cirrhosis and portal hypertension but without varices followed for a median of 51.1 months, those with a baseline HVPG <10 mmHg had a 90% probability of not progressing to the decompensated state during the follow-up period while the risk of decompensation was almost 6 times higher in the group ≥10 mmHg (unadjusted hazard ratio of 5.7; P<0.001) [10]. Studies indicate that mortality increases ~3% with every 1 mmHg increase in HVPG, such that a patient with an HVPG of 15 mmHg has a 30% greater risk of death than a patient with an HVPG of 5 mmHg (Figure 1) [10, 11].

Figure 1. Probability of Clinical Decompensation in Patients with Cirrhosis with and without Clinically Significant Portal Hypertension



Solid line: HVPG <10 mmHg; dotted line: HVPG ≥10 mmHg [10].

CSPH is accompanied with an increased risk for developing hepatic decompensation, including bleeding varices and formation of ascites. Esophageal varices form once the HVPG is ≥10 mmHg and are present in ~50% of patients with cirrhosis [12]. Variceal bleeding is a medical emergency and associated with a 10% to 30% mortality at 6 weeks [2, 7, 12]. Importantly, reducing the HVPG to <12 mmHg, or by at least 10-20%, significantly decreases the risk of variceal bleeding in both primary and secondary prophylaxis settings (for reviews, see [13-15]).

Patients with CSPH are also at risk for developing ascites. Ascites develops in ~50% of patients within 10 years of the diagnosis of cirrhosis [8]. Once ascites is present (with or without esophageal varices), the mortality rate is approximately 20% per year [7]. Mortality is greater when more than one complication is present [9] or when the patient progresses to a stage of "further" decompensation characterized by recurrent variceal hemorrhage/encephalopathy, refractory ascites, hyponatremia, and hepatorenal syndrome.

There is clearly a medical need for a drug that would either decrease the risk for developing decompensated cirrhosis in a patient with compensated cirrhosis or for a drug that would decrease the risk for a patient with a single decompensating event to develop further decompensation. This drug would result in an improvement in survival. In both cases, a drug that could decrease portal hypertension could be reasonably expected to achieve those goals.

Standard of Care for Management of Cirrhosis with Portal Hypertension

There are currently no medications approved for the treatment of cirrhosis or portal hypertension. However, non-selective beta blockers (NSBB) are the standard of care used in clinical practice to prevent variceal bleeding. The American Association for the Study of Liver Diseases recommends that NSBB be used in the following clinical settings [12]:

- Patients with cirrhosis and small varices that have not bled and who are at higher risk for bleeding (Child-Pugh B or C; red wale marks on Esophagogastroduodenoscopy [EGD])
- Patients with cirrhosis and medium/large varices that have not bled
- Patients with cirrhosis who survived an episode of acute variceal hemorrhage

NSBB appear to be effective at decreasing the risk of bleeding from esophageal varices in approximately one-third to one-half of patients [14, 16, 17]. However, bleeding from esophageal varices remains a significant clinical problem, even with the use of NSBB. While NSBB decrease the risk of variceal bleeding to low levels if the HVPG is lowered below 12 mmHg (~7% bleeding rate), few patients (less than 15%) achieve that goal [7]. For patients with at least a 20% reduction in HVPG who do not achieve an HVPG value <12 mmHg, the risk of bleeding remains substantial (bleeding rate ~29%) but is decreased approximately 50%. Clinically, the consequences of a variceal bleed are important. Variceal bleeding is a medical emergency and associated with a 10-30% mortality at 6 weeks [2, 7, 12].

NSBB act by decreasing portal flow but have no effect on improving intrahepatic circulation or improving liver function. For patients who continue to experience progressive cirrhosis, liver transplantation is the only other treatment option. In addition, NSBBs must be used cautiously in certain cirrhotic patient populations. For example, propranolol was prospectively shown to decrease survival in patients with refractory ascites [18]. These patients often have systemic hypotension, and the Baveno VI consensus conference recommended that patients with refractory ascites should be monitored closely when placed on NSBBs and that NSBBs should be reduced or discontinued in the presence of systolic blood pressure below 90 mmHg, hyponatremia with a serum sodium below 130 mEq/L, or acute kidney injury [2]. In addition, approximately 15-20% of patients do not tolerate NSBB [14, 17], and another 15% have a contraindication to NSBB use [12].

4.2 STUDY RATIONALE

Emricasan (IDN-6556) is a novel small molecule irreversible caspase inhibitor. Caspases are a family of intracellular cysteine protease inhibitors whose function is to mediate apoptosis, a type of programmed cell death, and activate some proinflammatory cytokines. Caspases cleave cytokeratin-18, an intracellular structural protein, during apoptosis in a very specific manner to produce caspase-cleaved cytokeratin-18 (cCK18), which is readily detected by a selective and commercially available antibody. Some caspases (e.g., caspase-1) can also process and activate pro-inflammatory cytokines such as interleukin-1β and interleukin-18. Caspases typically exist as pro-caspases and must be converted to an active form enzymatically. Activation of caspases in injured or pre-apoptotic cells leads to cleavage of a number of cell proteins, which ultimately results in cell death and activation of some pro-inflammatory cytokines. Caspase-mediated apoptotic and inflammatory pathways have been previously shown to play an important role in liver diseases, leading to the hypothesis that inhibition of

caspases may have significant therapeutic benefit for the treatment of liver fibrosis, independent of the underlying disease state (e.g. viral infection, fatty liver, etc.) [19]. Emricasan has been shown to be an effective inhibitor of liver injury and inflammation in several animal models of liver disease and to reduce portal hypertension in a model of cholestasis [20].

An additional emerging role of caspases is the formation and release of hepatocyte-derived microvesicles (also referred to as microparticles). Microvesicles are released by virtually all cells, but levels are increased in some pathologic states and different liver diseases, including alcohol, viral infection, and metabolic syndrome. Other processes that increase microvesicle release include oxidative stress, shear stress, systemic inflammation, and bacterial translocation. Many of these processes are present in patients with chronic liver disease, especially cirrhosis. Furthermore, microvesicles are believed to worsen portal hypertension by contributing to splanchnic vasodilation, angiogenesis, and vasoconstriction within the liver [21].

In support of the notion that caspase inhibition could have a beneficial role in portal hypertension, emricasan was recently shown to improve survival and decrease portal pressure in a murine model of portal hypertension [20]. Cholestasis followed by liver injury was induced by ligation of the common bile duct with resultant increase in portal pressure. Mice received either emricasan (10 mg / kg / day) or placebo for two weeks, with repeat measurement of portal pressure and removal of the liver for histological assessment. Emricasan treatment resulted in decreased microparticles and a statistically significant reduction in portal pressure, as well as a decrease in fibrosis, although the decrease in fibrosis did not reach statistical significance, suggesting that the effects on portal hypertension were at least in part independent of the anti-fibrotic effects of the drug. Importantly, emricasan treatment improved survival.

In non-cirrhotic patients with chronic liver disease due to two of the most common etiologies (chronic hepatitis C virus [HCV] infection and non-alcoholic fatty liver disease [NAFLD]), emricasan treatment decreased apoptosis biomarkers and improved transaminases. Emricasan treatment was associated with rapid and statistically significant reductions in elevated activated serum caspases and cCK18 in subjects with chronic HCV [22]. Importantly, emricasan reduced cCK18 levels to within the range typically observed in healthy subjects, but did not affect cCK18 levels in healthy subjects [23], indicating that emricasan can reduce elevated but not basal levels of apoptosis. Emricasan lowered transaminase levels within 1 week and maintained these reductions to 12 weeks in patients with chronic HCV infection [24]. Similarly, emricasan treatment (at a dose of 25 mg BID) significantly reduced alanine aminotransferase (ALT) levels in subjects with NAFLD and elevated ALT in a 28-day, placebo-controlled, multi-center study (Study IDN-6556-06).

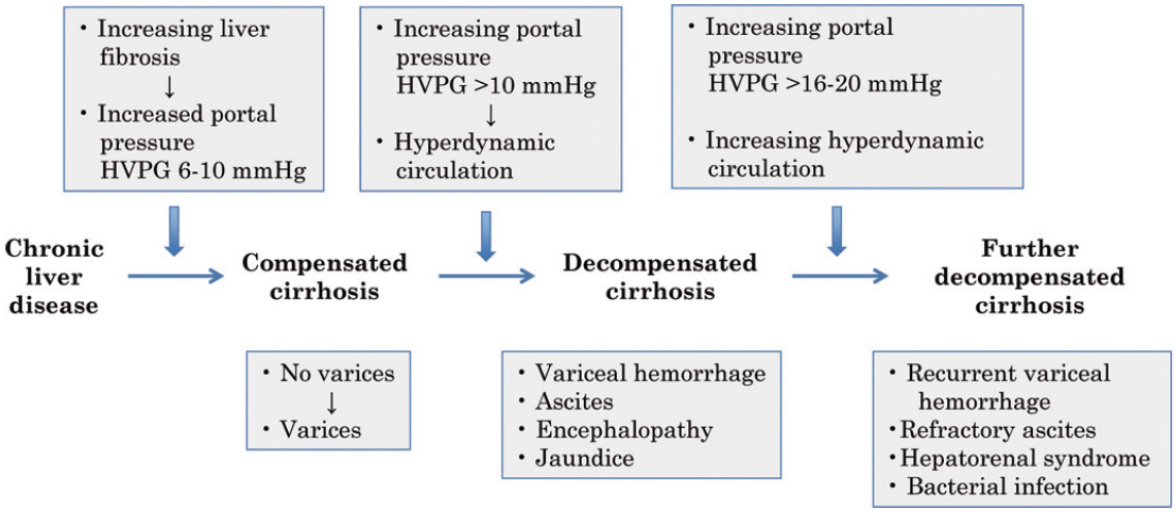
Based on the idea that caspases produce hemodynamically active, proinflammatory microparticles from apoptotic cells that could increase portal pressure by increasing intrahepatic resistance and/or decreasing splanchnic resistance, a recent open-label pilot study (Study IDN-6556-11) evaluated whether emricasan (at a dose of 25 mg twice daily [BID]) in patients with compensated cirrhosis (primarily due to non-alcoholic steatohepatitis [NASH] or HCV) and portal hypertension could lower portal pressure over 28 days. Of 23 subjects enrolled with baseline HVPG (5.5 to 32 mmHg), 22 subjects were evaluable for HVPG with data at baseline and Day 28. There was no significant difference in the HVPG response in the overall group, but analysis according to the recognized HVPG therapeutic threshold of 12 mmHg (indicative of severe portal hypertension) demonstrated a clinically meaningful mean (standard

deviation [SD]) decrease in HVPG of 3.7 (4.0) mmHg, representing a 17.2% decrease in the group with baseline HVPG ≥12 mmHg. Notably, 4/12 had a ≥20% decrease and 8/12 had a ≥10% decrease; 2/12 had a decrease in HVPG below 12 mmHg. Ten subjects with baseline HVPG <12 mmHg had a non-significant (p=0.12) mean (SD) increase of 1.9 (3.2) mmHg. Emricasan was overall well-tolerated with no drug-related serious adverse events (SAEs) and 1 subject discontinuing the study early for non-serious adverse events.

The reason for a robust decrease in HVPG in the ≥12 mmHg group and lack of discernable effect in the <12 mmHg group could be related to the differing pathophysiology of portal hypertension in these 2 groups. Figure 2, taken from a clinical review of portal hypertension [25], shows that as the HVPG increases to >10 mmHg and patients transition from compensated to decompensated cirrhosis, the hyperdynamic circulation becomes an increasingly important contributor to portal hypertension.

Portal hypertension is a dynamic process, and in early portal hypertension (HVPG 6-10 mmHg), the elevated pressures are largely due to increased intrahepatic resistance to blood flow as a result of both intrahepatic vasoconstriction and fibrotic changes associated with cirrhosis [26]. However, as cirrhosis and portal hypertension progress, splanchnic and systemic vasodilation, along with an increased cardiac output, dramatically increase portal venous blood flow [27, 28]. These observations explain why NSBBs, which decrease cardiac output and increase splanchnic resistance, are ineffective in patients with early stages of portal hypertension (HVPG <10 mmHg) when increased cardiac output and decreased splanchnic resistance are not yet contributing to the portal hypertension in those patients [29-31].

Figure 2. Natural History of Cirrhosis: Relationship with Increasing Portal Pressure [25]



Thus, there is sound preclinical and clinical rationale to believe that emricasan can decrease HVPG in subjects with NASH cirrhosis and severe portal hypertension, based on data in humans demonstrating the important pathophysiological role of excessive apoptosis and inflammation in cirrhosis and portal hypertension, as well as preclinical data showing that emricasan decreases apoptosis, inflammation, and fibrosis in mouse models of chronic liver

disease, and short-term (~1 month) data in humans with cirrhosis and severe portal hypertension demonstrating clinically meaningful reductions in HVPG with emricasan.

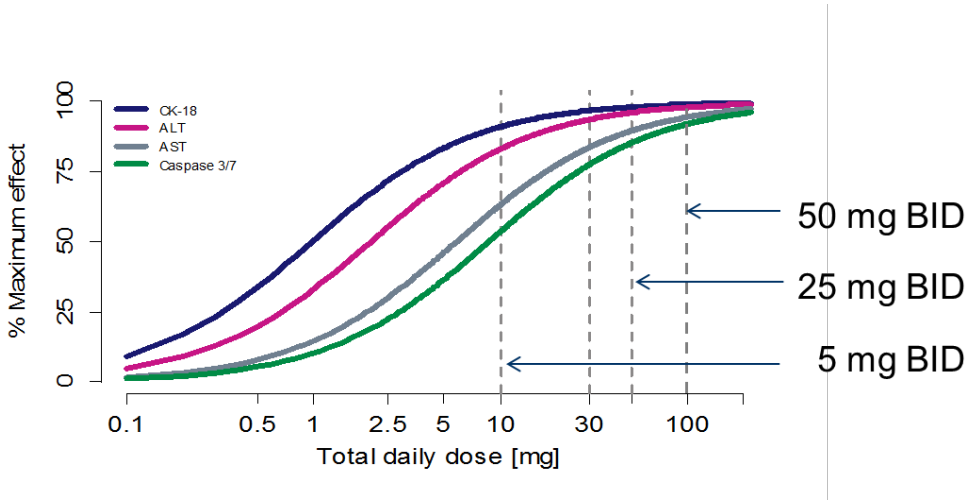
Dose Rationale

Emricasan has been administered to 624 subjects in 15 completed Phase 1 and 2 studies (including 169 healthy subjects, 394 subjects with elevated liver transaminases, 8 subjects with severe renal impairment, and 53 liver transplant subjects) with administration of single or multiple doses of intravenous or oral emricasan ranging from 0.1 to 10 mg/kg/day intravenously or 1 to 500 mg/day orally. Emricasan has been administered orally to 510 subjects, including 383 subjects with liver disease, most of whom received emricasan up to 50 mg BID for up to 3 months. Emricasan has generally been well tolerated with most adverse events being mild to moderate in severity, and the most common events (~3-5%) in subjects with liver disease receiving oral emricasan being fatigue, nausea, dizziness, and headache, without any clear relationship with dose or duration of therapy.

The relationship between emricasan dose and biomarker responses has been thoroughly characterized. The initial phase 1 and 2 studies assessed the effect of emricasan upon biomarkers at oral doses ranging from 0.5 mg BID up to 200 mg BID. The 0.5 mg BID dose was clearly active, decreasing cCK-18 and ALT by nearly 50%, but had less effect upon aspartate aminotransferase (AST) and caspase 3/7. Doses greater than 50 mg BID did not appear to have any greater reduction in biomarkers compared to the 50 mg BID dose. Having therefore defined the shape of the dose-response curve, subsequent clinical studies focused on the 5, 25 and 50 mg BID doses.

Formal dose-response modeling for emricasan used models based upon reductions of 4 biomarkers (ALT, AST, cCK18, and caspase 3/7). Dose response modeling in subjects with liver disease predominantly due to HCV who had normal hepatic function indicated that emricasan doses >27.6 mg twice daily (BID) provided the greatest probability of leading to significant reductions in serum transaminases (reflective of ongoing inflammation) and cCK18 (reflective of apoptotic activity) (Figure 3).

Figure 3. Dose-Response Modelling of Emricasan using Biomarkers



Dose (mg BID)	% of maximum response			
	CK-18	ALT	AST	Caspase 3/7
5	83.6	71.2	46.3	36.7
15	93.9	88.1	72.1	63.5
25	96.2	92.5	81.2	74.4

The biomarker dose-response curve was relatively flat between 0.5 to 50 mg BID, with doses as low as 5 mg BID showing near-maximal reduction for cCK-18 and ALT in subjects with normal hepatic function. Specifically, 5 mg BID reduced cCK18 and ALT by 71.2% to 83.6% of maximal but reduced AST and caspase 3/7 by only 36.7% to 46.3% of maximal. The 25 mg BID dosed reduced all 4 biomarkers by 74.4% to 96.2% of maximal, and the 50 mg BID showed incrementally greater reduction of AST and caspase 3/7. In addition, studies conducted in subjects with hepatic impairment (IDN-6556-08 and IDN-6556-02) suggested that the biomarker dose-response curve may be shifted to the right with severe hepatic impairment, and that the 50 mg dose might more effectively decrease biomarkers in those subjects than the 25 mg dose. Updating the dose response model with biomarker data from subjects with NAFLD indicated that the dose response for the NAFLD population was similar to that for the HCV population for subjects with elevated transaminases and normal hepatic function.

While the relationship between dose and biomarker response has been well-characterized, the relationship between emricasan dose and clinical responses has not been thoroughly assessed. Understanding that relationship is an important goal of the proposed phase 2b study. Pilot studies conducted only with the 25 mg BID dose of emricasan showed that this dose lowered portal vein pressures (HVPG) in subjects with severe portal hypertension following 1 month of treatment, and improved model for end stage liver disease [1] scores in subjects with baseline

MELD scores ≥15 following 3 months of treatment and provided the rationale to further explore the safety and efficacy of emricasan in patients with cirrhosis. To better understand the shape of the dose-response curve for clinically important endpoints (HVPG and MELD score) in subjects with cirrhosis and hepatic impairment (Child-Pugh classes A and B), the Sponsor intends to study the 5, 25 and 50 mg BID doses of emricasan.

Thus, the 5, 25, and 50 mg BID doses proposed for this Phase 2 study were chosen to evaluate a dose that is anticipated to be active but likely sub-maximal (5 mg BID) as well as a dose with a high likelihood of maximal efficacy based upon the biomarker dose-response curve (50 mg BID), with inclusion of an intermediate dose (25 mg BID) that has demonstrated efficacy on HVPG and MELD score in prior studies. This approach is reasonable given the large number of subjects exposed to repeat oral doses as high as 200 mg BID, good safety profile to date, lack of identified drug-related toxicities, and lack of tolerability issues at doses less than 500 mg (at which transient, mild GI symptoms were reported). Animal toxicology studies identified the gallbladder and intestines as having the potential for toxicity. However, careful assessment of pre- and post-dosing gallbladder ultrasound examinations and analysis of safety data for adverse events potentially related to either gallbladder or intestinal inflammation has revealed no evidence for a safety concern in humans to date.

5 STUDY OBJECTIVES

The objectives of this study are:

Primary Objective

- To assess whether emricasan compared to placebo leads to a mean decrease in hepatic venous pressure gradient (HVPG) at Week 24 in subjects with NASH cirrhosis and severe portal hypertension

Secondary Objectives

- To assess the safety and tolerability of emricasan
- To evaluate the dose response of emricasan on portal pressure as assessed by HVPG at Week 24
- To assess whether emricasan compared to placebo improves HVPG response at Week 24 using a 20% reduction from baseline response definition
- To assess whether emricasan compared to placebo decreases mechanism specific (caspase 3/7) and non-specific (ALT) biomarkers at Weeks 24 and 48

Exploratory Objectives

- To assess whether emricasan compared to placebo improves HVPG response at Week 24 using a 10% reduction from baseline response definition
- To assess whether emricasan compared to placebo improves liver function and prognosis at Weeks 24 and 48 as assessed by model for end-stage liver disease [1] and Child-Pugh (CP) scores (change in score, progression, regression)
- To assess whether emricasan compared to placebo improves biochemical and functional biomarkers (cCK18/M30, flCK18/M65, AST, total bilirubin, INR, and albumin) at Weeks 24 and 48
- To assess whether emricasan compared to placebo improves fibrosis markers at Weeks 24 and 48
- To assess whether emricasan compared to placebo improves health-related quality of life at Weeks 24 and 48
- To assess whether emricasan compared to placebo decreases development of decompensation or worsening of decompensation at Weeks 24 and 48
- To assess whether emricasan compared to placebo improves liver metabolic function at Weeks 24 and 48 as assessed by methacetin breath test (at select sites)
- To assess whether emricasan compared to placebo improves liver stiffness at Weeks 24 and 48 as assessed by transient elastography (FibroScan®) (at select sites)

6 STUDY DESIGN

This is a multicenter, double-blind, randomized, placebo-controlled, dose-response study to evaluate the safety and efficacy of emricasan in improving portal hypertension in subjects with NASH cirrhosis and severe portal hypertension (defined as HVPG ≥12 mmHg). Subjects can have compensated (at least 60% of subjects but no more than 75%) or decompensated cirrhosis with no more than 1 prior significant decompensating event and must be currently clinically stable on stable standard therapy [2] (see Inclusion/Exclusion Criteria). Randomization will be stratified by compensated vs. decompensated status at baseline as well as use of non-selective beta-blockers (NSBB) or not. Subjects who are otherwise eligible will undergo the HVPG procedure as the last qualifying procedure prior to Day 1.

The study treatment duration will be up to 48 weeks, including an initial 24-week randomized treatment phase with follow-up HVPG at Week 24 (primary endpoint) and an additional 24-week treatment phase (continuing the same study drug treatment as initially randomized). Subjects completing the initial 24-week randomized treatment phase will be re-consented for the additional 24-week treatment phase. HVPG measurements will be performed at screening and Week 24, with additional placebo controlled safety follow-up and exploratory efficacy assessments through Week 48. Subjects will complete a final follow-up visit approximately 2 weeks after the end of treatment (i.e., at Week 26 if completing the initial 24-week randomized treatment only or at Week 50 if completing the 48-week treatment).

Subjects with baseline HVPG ≥12 mmHg may experience progression of cirrhosis during the 48-week study. Given that the primary endpoint for this study is HVPG rather than a clinical event (or clinical composite), subjects who have a decompensating event or worsened decompensation during the study will not be required to withdraw and can remain in the study unless the investigator feels the subject is not stable or the subject requires a transjugular intrahepatic portal shunt or other portosystemic bypass procedure, which would confound the HVPG assessment. Subjects who progress to Child-Pugh C will be withdrawn from study drug but are expected to remain in the study and complete all planned study visits (see Section 8.1.7). All subjects who wish to discontinue study drug treatment should remain in the study and complete all planned study visits, in order to minimize missing data and protect the integrity of the study results. Subjects who withdraw consent for participating in the study should discontinue study visits. Subjects for whom the investigator deems that it is not in the best interest of the subject to continue participating in the study may also discontinue study visits.

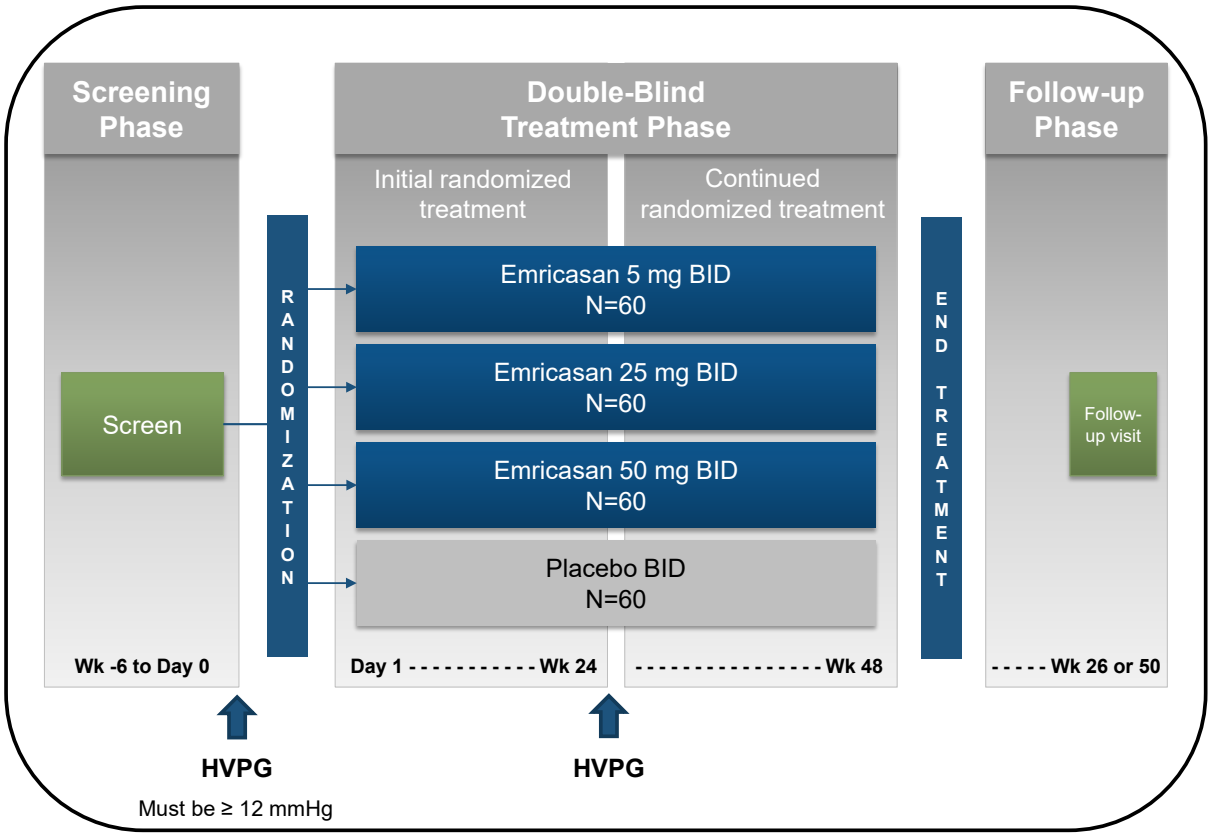
Subjects will be randomized in a 1:1:1:1 ratio to emricasan 50 mg BID, emricasan 25 mg BID, emricasan 5 mg BID or matching placebo BID.

For each subject, the study will consist of:

- Screening period of up to 6 weeks
- Double-blind treatment period of 24 or 48 weeks
- A follow-up visit 2 weeks after the Week 24 or Week 48 (or early termination) visit

The duration of each subject's participation will be approximately 32 or 56 weeks.

Figure 4. Study Schema



Appendix I, Schedule of Events*, indicates which procedures and evaluations will be performed throughout the study. An overview of key events is described below.

Screening Phase (Week -6 to Day 0)

Subjects will undergo a Screening period of up to 6 weeks; however, the screening could be completed within a shorter time frame. Subjects will sign an ICF before any study-related procedures are performed. Subjects will be screened to determine their eligibility. Medical/surgical history, medication record (prior and concomitant medications and therapy), and a physical examination including vitals will be obtained for all subjects. A series of laboratory and diagnostic tests will be performed. In general, a qualifying HVPG should be the last assessment performed during the Screening phase prior to randomization and should only be performed in subjects who meet all other eligibility criteria.

*If any discrepancies should be found between the text of the protocol and Appendix I, Schedule of Events, the table will predominate.

Initial 24-Week Double-Blind Treatment Phase (Day 1 to Week 24)

All subjects will be evaluated regularly through study visits every 4 weeks and laboratory and diagnostic tests for safety and efficacy as described in Appendix I, Schedule of Events.

Continued 24-Week Double-Blind Treatment Phase (Week 25 to Week 48)

Subjects consenting for continued treatment (continuing the same study drug treatment as initially randomized) will be evaluated regularly through study visits every 8 weeks and laboratory and diagnostic tests for safety and efficacy as described in Appendix I, Schedule of Events. Subjects can be seen more frequently for clinical reasons if indicated, but study assessments do not need to be performed at visits that are solely for clinical care.

Follow-up Phase (Approximately 2 weeks after Week 24 or Week 48)

Subjects will return approximately 2 weeks after completing Week 24 or Week 48 for a follow-up visit (either at Week 26 or Week 50). The visit will include study assessments as specified in the Schedule of Events. This is the final study visit for all subjects. The end of the trial will be when the last subject completes the last follow-up visit.

All subjects who prematurely discontinue the study, regardless of the cause, should undergo a follow-up visit (see Section 8.7.1) approximately 2 weeks following the early discontinuation visit.

7 STUDY POPULATION

7.1 INCLUSION CRITERIA

To participate in this study, subjects must meet **all** of the following criteria:

1. Male or female subjects 18 years or older, able to provide written informed consent and able to understand and willing to comply with the requirements of the study.
2. Cirrhosis due to NASH with exclusion of other causes of cirrhosis (e.g. chronic viral hepatitis, alcoholic liver disease, etc.)
   - Diagnosis of cirrhosis is based on:
     - Biopsy OR
     - Clinical evidence: platelet count <150,000, AST > ALT, and either nodular liver surface on imaging or splenomegaly
   - NASH is based on at least 1 of the following:
     - Prior or current biopsy showing steatohepatitis (fat, ballooning degeneration, inflammation) consistent with NASH
     - At least 2 metabolic risk factors for at least 5 years preceding the diagnosis of cirrhosis: diabetes mellitus, impaired fasting glucose, obesity (Body Mass Index (BMI) ≥30 kg/m^2 or central obesity), hypertension, dyslipidemia (See Appendix IV)
     - Prior or current biopsy showing some but not all diagnostic features of NASH (e.g. only fat or ballooning degeneration or inflammation) but with no evidence for viral hepatitis or other liver disease AND either fatty liver disease on prior imaging or at least 1 metabolic risk factor (as above) for at least 5 years preceding the diagnosis of cirrhosis

   Note: Previous viral hepatitis that was curatively treated (with sustained viral response) is not an exclusion as long as: 1) viral eradication was achieved at least 3 years prior to the diagnosis of cirrhosis and 2) all other criteria are met for NASH as the etiology of cirrhosis
3. Compensated cirrhosis (no history of or presence of clinically evident ascites, variceal hemorrhage, or encephalopathy, and on no medications to treat these complications)

   OR

   Decompensated cirrhosis with no more than 1 prior significant decompensating event:
   a. If prior decompensating event was variceal hemorrhage, event must have occurred at least 3 months prior to Day 1
   b. If prior decompensating event was ascites requiring chronic diuretics, ascites should be well controlled (not clinically evident, i.e. no ascites or ascites only detectable by ultrasound examination) on a stable dose of diuretics for at least 3 months prior to Day 1
   c. If prior decompensating event was hepatic encephalopathy ≥ grade II or requiring hospitalization, encephalopathy should be well-controlled (Stage 0 or 1) on stable medication for at least 3 months prior to Day 1

Note: Previous transient ascites or hepatic encephalopathy in a subject who is currently stable without clinically evident ascites or encephalopathy and on no medications for these conditions does not count as a prior significant decompensating event

4. Severe portal hypertension defined as HVPG ≥12 mmHg (see Section 8.4.1 for recommendations to identify subjects more likely to meet the HVPG criteria)
5. Subjects who are on NSBB, nitrates, diuretics, lactulose, rifaximin, or statins must be on a stable dose for at least 3 months prior to Day 1
6. Willingness to utilize effective contraception (for both males and females of reproductive potential) from Screening to 4 weeks after the last dose of study drug
7. Platelet count ≤125 k/mm^3 or transient elastography ≥20 kilopascal [3] during screening
8. If on therapeutic dose of vitamin E, stable for 6 months prior to Day 1

7.2 EXCLUSION CRITERIA

Subjects who meet **any** of the following criteria will be excluded from the study:

1. Evidence of severe decompensation, defined as:
   - Presence or history of more than one type of significant decompensating event (clinically evident ascites requiring chronic diuretics, variceal hemorrhage, and/or overt encephalopathy)

     Note: Previous transient ascites or hepatic encephalopathy in a subject who is currently stable without clinically evident ascites or encephalopathy and on no medications for these conditions does not count towards this exclusion (See Inclusion Criteria #4).

   - One type of decompensating event with the following characteristics:
   - More than 1 episode of variceal hemorrhage or bleeding from a portal hypertensive source (e.g. portal hypertensive gastropathy)
   - Ascites that has required more than 1 large-volume paracentesis (>5 L) for treatment or that has been complicated by spontaneous bacterial peritonitis, hyponatremia (serum Na <130), and/or hepatorenal syndrome
   - More than 1 episode of overt hepatic encephalopathy requiring hospitalization

2. Severe hepatic impairment defined as a Child-Pugh score ≥10
3. ALT >3 times upper limit of normal (ULN) or AST >5 times ULN during screening
4. Estimated creatinine clearance <30 mL/min
5. Prior transjugular intrahepatic portosystemic shunt or other porto-systemic bypass procedure
6. Known portal vein thrombosis
7. Symptoms of biliary colic, e.g. due to symptomatic gallstones, within the last 6 months, unless resolved following cholecystectomy, other definitive treatment (e.g., sphincterotomy), or medical management (e.g., ursodeoxycholic acid)

8. Current use of medications that are considered inhibitors of OATP1B1 and OATP1B3 transporters: atazanavir, cyclosporine, eltrombopag, gemfibrozil, indinavir, lopinavir, ritonavir, rifampin, saquinavir, simeprevir, telaprevir, tipranovir, or some combination of these medications
9. Alpha-fetoprotein >50 ng/mL
10. History or presence of clinically concerning cardiac arrhythmias, or prolongation of screening (pre-treatment) QT Interval Corrected by the Fridericia Correction Formula (QTcF) interval of >500 msec
11. History of or active malignancies, other than those successfully treated with curative intent and believed to be cured
12. Significant systemic or major illness other than liver disease that in the opinion of the investigator would preclude the subject from participating in and completing the study, including but not limited to acute coronary syndrome or stroke within 6 months of screening or major surgery within 3 months of screening
13. Prior liver transplant
14. Change in diabetes medications within 3 months of screening, including initiation, discontinuation, or change in dose except for medications titrated according to blood glucose
15. Uncontrolled diabetes mellitus (HbA1c >9%) within 3 months of screening
16. Restrictive bariatric surgery or bariatric device within 1 year of screening or prior malabsorptive bariatric surgery
17. Known human immunodeficiency virus infection
18. Use of controlled substances (including inhaled or injected drugs) or non-prescribed use of prescription drugs within 1 year of screening to the point of interfering with the subject's ability to comply with study procedures and study drug administration in the investigator's judgement
19. History of significant alcohol consumption (>20 g/day for females and >30 g/day for males on average) within the past 5 years
20. If female: planned or known pregnancy, positive urine or serum pregnancy test, or lactating/breastfeeding
21. Previous treatment with emricasan or active investigational medication (except methacetin) in a clinical trial within 3 months prior to Day 1

7.3 SUBJECT IDENTIFICATION

During the screening period, subjects will be identified by a unique screening number composed of the 3-digit site number and a 2-digit subject identification number that starts with 01. On Day 1, subjects who will be randomized will be identified by a unique 4-digit randomization number. Only qualified subjects will be assigned a randomization number.

7.4 RANDOMIZATION PROCEDURE

The assignment to emricasan or placebo will be performed randomly. The randomization schedule will be generated using a validated randomization program and verified for accuracy using strict quality control procedures.

The assignment of randomization number and treatment assignment will be centrally coordinated through the study's Interactive Web Randomization System (IWRS). Randomization numbers will be assigned by the IWRS. The IWRS will notify sites when enrollment for compensated subjects reaches 75% or enrollment for decompensated subjects reaches 40%.

The randomization will be stratified by 2 factors:

- Compensated vs. decompensated status at baseline
- Use of non-selective beta-blockers (NSBB) or not

7.5 BLINDING/UNBLINDING PROCEDURES

Investigators will be able to unblind subjects through the IWRS when it is medically imperative to know whether a subject is receiving emricasan or placebo, such as in the event of an adverse event (AE) that the Investigator feels cannot be adequately treated without knowing the identity of the study drug. Every effort must be made to contact the Medical Monitor to discuss the case before breaking the blind, or if in an emergency, as soon as possible thereafter (no later than 24 hours after emergency unblinding) to inform the Medical Monitor that unblinding was performed but without disclosing the actual treatment assignment. Investigator should make arrangements to ensure that access to the secure internet site (i.e., individual user name and password) is maintained in strict confidence to prevent a compromise of subject blinding by non-study or unauthorized individuals.

The Sponsor may access the randomization codes for subjects with potential suspected unexpected serious adverse reactions (SUSARs) for the purpose of regulatory reporting or for the purpose of evaluating an emergent safety issue. In such an event, the Sponsor will document the rationale, circumstances, and the person or persons being informed about the unblinding.

If the blind for a subject is broken (by the Investigator or the Sponsor), an entry must be made in the electronic data capture system that contains the reason that the blind was broken and the name of the person contacted at the Sponsor or designee. If the Investigator becomes unblinded to a subject's study drug assignment, the subject should be withdrawn from the study.

8 STUDY ASSESSMENTS AND CONDUCT

8.1 SAFETY ASSESSMENTS

8.1.1 Adverse Events

Adverse events verbatim terms will be collected at each study visit. The start date of the event, stop date of the event (if known), severity, relationship to study drug (emricasan or placebo) or to methacetin, seriousness, outcome, and action taken for each verbatim term will also be collected. All verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary for purposes of summarization. AEs (except SAEs, see Section 13.8) should be collected for a subject starting from signing of the informed consent until the subject's last study visit (follow-up visit, early termination, or last regularly scheduled study visit).

8.1.2 Medical History and Physical Examinations

Medical and surgical history will be taken at screening. A comprehensive physical examination will be performed at the Screening, Week 24, and Week 48 visits including examination of: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen (including liver and spleen examination), extremities, and nervous system. A focused physical examination limited to relevant assessments and based on any symptoms or concerns related to a particular body system will be performed at all other visits. Weight, assessed in street clothes with shoes and outerwear off, and height (screening visit only) will be recorded at the specified visits. Each subject's body mass index (BMI) will be calculated. Assessment of Child-Pugh clinical features will be performed at all visits.

8.1.3 Vital Sign Measurements

Respiratory rate, pulse, systolic and diastolic blood pressure, and temperature measurements ('vital signs') will be performed. Evaluation of the respiratory rate will be measured by counting the inhalations for one minute. Blood pressure and heart rate measured during the HVPG procedure will also be collected.

8.1.4 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be performed at Screening and at subsequent visits, as specified in the Schedule of Events. Original ECGs with interval printouts and rhythm strips run at 25 mm/sec must be provided as source documentation.

Automatically calculated QTc intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If clinically significant findings occur as determined by the Investigator, the Medical Monitor should be contacted.

8.1.5 Monitoring for Potential Gallbladder Adverse Effects

Due to pre-clinical findings that emricasan was associated with gallbladder inflammation, specific safety evaluation and monitoring procedures will be followed.

- Subjects with symptoms of biliary colic, e.g. due to symptomatic gallstones, within the last 6 months, unless resolved following cholecystectomy, other definitive treatment (e.g., sphincterotomy), or medical management (e.g., ursodeoxycholic acid), will be excluded from the study.
- All subjects will have a comprehensive liver and gallbladder ultrasound (including examination of the biliary tree, assessment of whether gallbladder wall thickening is present, and measurement of gallbladder wall thickness) at the Screening visit, unless the subject had an ultrasound within 3 months of Screening that captures all the assessments noted above. If source documentation is provided, the prior ultrasound can be used in place of the Screening ultrasound. An anonymized copy of the report (and images if needed) from the ultrasound (whether historical or performed for the study) should be provided to the Sponsor.
- At each study visit, the Investigator will specifically assess the subject for any symptoms consistent with biliary colic, e.g. sharp right upper quadrant pain, nausea, vomiting, fever (with cholecystitis), etc. If the subject reports symptoms of biliary colic or other symptoms suggestive of gallbladder disease on directed questioning or spontaneously reports such symptoms at any other time during the study, a follow-up liver and gallbladder ultrasound (including assessment of the biliary tree and any gallbladder abnormalities) should be performed. If additional ultrasounds (or other imaging) are performed during the study for evaluation of biliary colic, assessment of the gallbladder as noted above should be performed, and an anonymized copy of the report(s) (and images if needed) should be provided to the Sponsor.
- Symptoms of biliary colic or other symptoms suggestive of gallbladder disease (such as cholecystitis) that trigger a follow-up ultrasound should be recorded as AEs that are possibly or probably related to study drug.

8.1.6 Monitoring for Evidence of Potential Drug-Induced Liver Injury (DILI)

Liver transaminases (ALT, AST) and total bilirubin will be monitored regularly (assessed at each study visit) during the study not only as mechanism-independent biomarkers of inflammation, but also for any evidence of potential DILI. Given that the patient population to be studied has underlying liver disease and therefore is likely to have abnormalities in liver transaminases and/or bilirubin at baseline, the guidelines for DILI monitoring in this study have been adapted from the US Food and Drug Administration (FDA) guidance on DILI that was based primarily on monitoring subjects with normal liver enzymes and bilirubin at baseline and incorporate suggestions provided to the Sponsor from the FDA regarding monitoring for DILI in subjects who have abnormal baseline values of liver transaminases and/or total bilirubin.

Table 1. Liver Monitoring Procedure

	Additional Monitoring ONLY	Additional Monitoring AND Study Medication Interruption
Criteria	**If any ONE of the following 2 criteria are met:** • Isolated increase in ALT or AST and minimal or no increase in total bilirubin (TB) in the absence of clinical hepatitis symptoms (including but not limited to fever, anorexia, nausea, vomiting, abdominal pain, rash) ○ ALT >2x baseline if baseline ALT >2x ULN OR ○ ALT >3x ULN if baseline ALT ≤2x ULN OR ○ AST >2x baseline if baseline AST >2x ULN OR ○ AST >3x ULN if baseline AST ≤2x ULN ○ No increase in TB greater than criteria below • Isolated increase in TB and minimal or no increase in ALT or AST in the absence of clinical hepatitis symptoms (as described above) ○ TB >2x baseline if baseline TB >ULN *OR* ○ TB >2x ULN if baseline TB ≤ULN ○ No increase in ALT or AST greater than criteria above	**If any ONE of the following 6 criteria are met:** • Isolated transaminase increase ○ ALT *OR* AST > 8x ULN • Increase in TB that is related to an increase in direct bilirubin (defined as a direct bilirubin to TB ratio >35%) ○ TB increase >2.0 mg/dL if baseline TB >2.0 mg/dL *OR* ○ TB >2x baseline or >1.5x ULN, whichever is higher, if baseline TB ≤2.0 mg/dL • Increases in transaminases and TB ○ ALT >3x baseline if baseline ALT >ULN *OR* ○ ALT >5x ULN if baseline ALT ≤ULN *OR* ○ AST >3x baseline if baseline AST >ULN *OR* ○ AST >5x ULN if baseline AST ≤ULN AND ○ TB >2x baseline if baseline TB >ULN *OR* ○ TB >2x ULN if baseline TB ≤ULN • Increase in cholestatic marker (ALP) when the ALP increase is due to a hepatic source ○ ALP >2x baseline if baseline ALP >ULN *OR* ○ ALP >3x ULN if baseline ALP ≤ULN • Increase in INR that is refractory to vitamin K administration in the absence of a clear reason (e.g. initiation of anticoagulants that can affect INR) ○ INR increase of >0.4 if baseline INR >ULN *OR* ○ INR increase to >1.5 if baseline INR ≤ULN • Any increase in transaminases or TB if associated with symptoms (e.g., fever, anorexia, nausea, vomiting, abdominal pain, rash) and/or >5% eosinophilia

Confirmation of Need for Additional Liver Monitoring	**If either of above criteria met:**
	• Repeat liver profile (AST, ALT, total and direct bilirubin, GGT, alkaline phosphatase, albumin, CBC, and INR) within 2 to 3 days to confirm the elevation
	  ○ If a subject lives in a remote area, use of local labs may be approved by the Sponsor
	  ○ The Investigator will ensure that local lab results are promptly reviewed
	• If not confirmed, resume routine laboratory testing
		If any of above criteria met:
		• Repeat liver profile (AST, ALT, total and direct bilirubin, GGT, alkaline phosphatase, albumin, CBC, and INR) within 2 to 3 days to confirm the elevation
		  ○ If a subject lives in a remote area, use of local labs may be approved by the Sponsor
		  ○ The Investigator will ensure that local lab results are promptly reviewed
		• If not confirmed, resume routine laboratory testing

Study Medication Interruption	Not applicable	**If elevated tests confirmed:** • Interrupt study medication
Work-up for Liver Injury	**If elevated tests confirmed:** • Initiate work-up for other causes of liver injury (see below)	**If elevated tests confirmed:** • Initiate work-up for other causes of liver injury (see below)

Close Monitoring	**<u>If elevated tests confirmed:</u>**
	• Monitor the subject with laboratory testing 2 or 3 times weekly with the frequency of testing decreased to once a week or less if abnormalities stabilize and the subject is asymptomatic
	  ○ If a subject lives in a remote area, use of local labs may be approved by the Sponsor
	  ○ The Investigator will ensure that local lab results are promptly reviewed
	• Discontinue frequent lab monitoring and resume usual study visit monitoring schedule when
	  ○ ALT and AST decrease to <1.2x baseline (or <1.2x ULN if baseline value <ULN) on two consecutive measurements
	  ○ TB decreases to <1.3x baseline (or <1.3x ULN if baseline value <ULN) on two consecutive measurements
	• Clinical judgment should determine the intensity and duration of close monitoring for subjects who are clinically stable and asymptomatic but with elevated test(s)
		<u>If elevated tests confirmed:</u>
		• Monitor the subject with laboratory testing 2 or 3 times weekly with the frequency of testing decreased to once a week or less if abnormalities stabilize and the subject is asymptomatic
		  ○ If a subject lives in a remote area, use of local labs may be approved by the Sponsor
		  ○ The Investigator will ensure that local lab results are promptly reviewed
		• Discontinue frequent lab monitoring and resume usual study visit monitoring schedule when
		  ○ ALT, AST, ALP decrease to <1.2x baseline (or <1.2x ULN if baseline value <ULN) on two consecutive measurements
		  ○ TB, INR decreases to <1.3x baseline (or <1.3x ULN if baseline value <ULN) on two consecutive measurements
		• Clinical judgment should determine the intensity and duration of close monitoring for subjects who are clinically stable and/or asymptomatic but with elevated test(s)

Potential Restart of Study Medication after Interruption	Not applicable	• In accordance with the FDA "Guidance for Industry Drug Induced Liver Injury (DILI): Premarketing Clinical Evaluation"
		  ○ If a subject has suspected DILI, restarting study medication is NOT recommended
		• If DILI is considered unlikely AND liver tests return to levels indicated above for discontinuing close monitoring
		  ○ Restarting study medication may be considered according to the discretion of the Investigator and after discussion with the Sponsor

Follow-up During Restart of Study Medication after Interruption	Not applicable	• Laboratory tests (as noted above for confirmatory testing) should be checked within 2-3 days after restarting study medication, followed by weekly lab tests for 2-4 weeks (depending on Investigator judgment) and then monthly for 3 months, which may occur at regular study visits • Any subject who meets the criteria for liver monitoring (after confirmatory testing) a second time will have study medication permanently discontinued

If elevated tests are confirmed, the following work-up should be performed at the first monitoring visit:

- Obtain a more detailed history of symptoms and prior and concurrent diseases
- Obtain further history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtain a history for exposure to environmental chemical agents and travel
- Obtain serology for viral hepatitis (hepatitis A immunoglobulin M [IgM], HBV surface antigen, HCV antibody, hepatitis E IgM, cytomegalovirus IgM, Epstein Barr virus antibody panel) and autoimmune hepatitis (e.g. anti-nuclear antibody)
- Perform further testing for Gilbert's if appropriate (e.g. if total bilirubin is elevated)

8.1.7 Management of Subjects Who Progress to Child-Pugh C

Subjects with Child-Pugh C status at baseline will be excluded. Child-Pugh status will be assessed at each visit during the study, and subjects who progress to Child-Pugh C will be considered for withdrawal from study drug treatment. However, given the day to day fluctuations in clinical laboratory parameters (total bilirubin, albumin, INR) that could transiently change a subject's Child-Pugh status to C, a Child-Pugh C score should be confirmed on repeat testing and evaluation before withdrawing study drug treatment. Laboratory tests and clinical evaluation consistently confirming Child-Pugh C status should lead to study drug withdrawal. Subjects should, however, remain in the study and complete all scheduled study visits.

If post-baseline Child-Pugh score is ≥10

- Subject should return for repeat laboratory testing (total bilirubin, albumin, INR) and clinical evaluation (ascites, hepatic encephalopathy) ideally within 3 days of the tests consistent with Child-Pugh C status but at least within 7 days
  - If repeat Child-Pugh score (2nd test) is <10, the subject should continue study drug treatment with the next follow-up occurring at the next regularly scheduled study visit.
  - If repeat Child-Pugh score (2nd test) is ≥11, the subject should be withdrawn from the study drug, but should complete all scheduled study visits.
  - If repeat Child-Pugh score (2nd test) is 10 and the investigator feels the subject is clinically stable to continue study drug treatment, the subject should return for repeat laboratory testing (total bilirubin, albumin, INR) and clinical evaluation (ascites, hepatic encephalopathy) in 1-2 weeks
    - If repeat Child-Pugh score (3rd test) is ≥10, the subject should be withdrawn from the study drug, but should complete all scheduled study visits.
    - If repeat Child-Pugh score (3rd test) is <10, the subject should continue study drug treatment with the next follow-up occurring at the next regularly scheduled study visit.

8.1.8 Screening and Follow-up Questionnaires for Alcohol Abuse

The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire developed to screen for excessive drinking, helping to identify whether a person has hazardous (or risky) drinking, harmful drinking, or alcohol dependence. The AUDIT-C is a 3-question version of AUDIT that performed similarly to the full AUDIT for detecting heavy drinking and/or active abuse or dependence [32].

The Skinner Alcohol Dependence scale is a 25-item questionnaire that provides a quantitative measure of the severity of alcohol dependence, with scores in the 1st, 2nd, 3rd, and 4th quartiles corresponding to low, intermediate, substantial, and severe levels of alcohol dependence being likely.

The AUDIT and Skinner Alcohol Dependence scale will be used during Screening to screen for any evidence of alcohol abuse, and the AUDIT-C will be used during the treatment phase of the study to monitor for any evidence of active alcohol abuse.

8.1.9 Screening Esophagogastroduodenoscopy (EGD)

An EGD will be performed during screening, unless the subject had a prior EGD performed within an acceptable time frame according to the recommendations outlined in the Baveno VI Consensus Workshop on portal hypertension [2], and records from the prior EGD are available. For example, if there is ongoing liver injury (e.g. NASH), patients with compensated cirrhosis with no varices on screening EGD should have surveillance endoscopy at 2-year intervals while patients with decompensated cirrhosis and small varices should have surveillance endoscopy at 1-year intervals. Subjects with medium or large varices or with decompensated cirrhosis should have surveillance endoscopy at 1-year intervals.

The following information should be available from the EGD: presence or absence of esophageal varices, size of varices (small, medium, large), and any high-risk stigmata (e.g. red wale signs). Small varices are defined as those that barely protrude above the esophageal mucosa but that persist after air insufflation of the esophagus, large varices are those that occupy half of the esophageal lumen, and medium-sized varices are those that are intermediate between small and large.

If the Investigator deems it medically necessary, additional EGDs other than those specified by the protocol may be performed during the study. If additional EGDs are performed during the study, the reasons for and results of the additional EGDs will be captured as study data.

8.2 EFFICACY ASSESSMENTS

8.2.1 Hepatic Venous Pressure Gradient (HVPG)

The HVPG is the difference between wedged (or occluded) hepatic vein pressure (WHVP) and free hepatic vein pressure (FHVP) and represents the gradient between the portal vein and the intra-abdominal inferior vena cava (IVC) pressure, with normal HVPG being 3-5 mmHg. It is a measure of intrahepatic sinusoidal pressure that correlates directly with direct measurements of portal pressure in cirrhosis.

Measurement of the HVPG is a moderately invasive procedure that involves insertion of a catheter via the right internal jugular vein to measure WHVP and FHVP. The WHVP is obtained by inflating a balloon at the tip of the catheter to occlude the lumen of the hepatic vein (preferably the main right hepatic vein). The FHVP is obtained by deflating the balloon of the hepatic vein catheter and is very close to the IVC pressure. If the difference between FHVP and IVC is ≥2 mmHg, this usually reflects the catheter advanced too far into the hepatic vein. The FHVP should be obtained with the catheter tip 1-3 cm into the hepatic vein; if the point of adequate balloon occlusion is further down the hepatic vein, FHVP should be repeated at this "withdrawn" position. The WHVP and FHVP are affected equally by intra-abdominal pressure (e.g. increased intra-abdominal pressure in ascites), whereas their gradient (HVPG) is not. Therefore, the measurement of HVPG incorporates its own zero reference point and is not affected by increases in intra-abdominal pressure. Furthermore, the use of the HVPG eliminates another very important source of error, the external zero reference point, which should be placed at the level of the mid-axillary line and kept constant during the study.

Practical Considerations for HVPG Measurement

- The procedure is an outpatient procedure (median duration of ~25 minutes) that is generally well-tolerated and usually associated with minimal complications (mostly hematoma and/or pain at site of puncture).
- WHVP can also be measured by advancing the catheter into the smallest branch of the hepatic vein and "wedging" it, but this is less accurate than the "occluded" pressure because the balloon catheter occludes a larger hepatic venous branch and can, theoretically, measure WHVP over a wider vascular territory of the liver compared with a wedged catheter.
- The test should be performed preferably in the morning because there is circadian variation of the HVPG (higher during the day, lower at night). For a given subject, the Screening and Week 24 tests should be performed at approximately the same time of the day, i.e. after fasting in the morning.
- The test should be performed after an overnight fast as the HVPG increases after food ingestion (1-2 hours post-prandial), particularly in cirrhosis.
- The procedure may be done under slight conscious sedation with intravenous midazolam, but deep sedation (e.g. with opioids such as fentanyl) must be AVOIDED as it can lead to artifacts caused by exaggerated deep breathing.
- At least three sets of WHVP (with continuous recording at least 60 sec [or longer if the pressure is still increasing]) and FHVP (with recording at least 20-30 sec) measurements should be collected, with the average used to calculate the final HVPG result.
- Adequate occlusion of the hepatic vein should be checked by injecting a small amount (0.5 mL) of contrast dye with the balloon inflated.
- After the WHVP and FHVP measurements are obtained, 3 additional pressure measurements should be collected as the catheter is being withdrawn (and without interrupting the recording): a) at the most proximal portion of the hepatic vein (juncture between IVC and hepatic vein), at the IVC (at the level of the hepatic vein) and at the right atrium.

HVPG will be performed at Screening and Week 24 visits. A blood sample from the hepatic vein and a paired systemic sample (obtained from the jugular vein through the side arm of the venous introducer) will be collected for measurement of biomarkers.

Generally, the HVPG should be the last assessment performed during the Screening phase prior to randomization and should only be performed in subjects who fulfill all other inclusion criteria. A central reader appointed for this study will ensure that all participating sites are qualified to perform the procedure. Original tracings of the pressure measurements will be kept at the site as part of source documentation for the study, and redacted copies will be forwarded to the Central Reader for evaluation. A manual providing more details on the HVPG procedure will be provided to sites.

8.2.2 Model for End Stage Liver Disease [1] Score

The Model for End-Stage Liver Disease, or MELD, is a scoring system for assessing the severity of chronic liver disease and short-term mortality. An earlier version of the formula for

MELD used the subject's values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time and was calculated according to the following formula (rounded to the nearest whole number):

Previous MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43

If the patient was dialyzed twice within the last 7 days, then the value for serum creatinine used was set to 4.0. Any value less than 1 was given a value of 1 (i.e. if bilirubin was 0.8, a value of 1.0 was used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result).

In January 2016, the Organ Procurement and Transplantation Network updated the MELD score to include sodium for the purpose of liver organ allocation. Thus, the MELD score is now calculated based on the previous MELD score (provided above) as well as sodium (Na) according to the following formula (which will be the one used for the purpose of this study):

MELD = previous MELD + 1.32 × (137-Na) – [0.033 × previous MELD × (137-Na)]

Sodium values <125 mmol/L will be set to 125, and values >137 mmol/L will be set to 137.

8.2.3 Child-Pugh Score and Classification

The Child-Pugh score (sometimes referred to as the Child-Turcotte-Pugh score) is used to assess the prognosis of chronic liver disease and is calculated as the sum of five component scores. Total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy components are scored with values of 1 to 3 points with 3 indicating the greatest severity. This provides a Child-Pugh score of 5 to 15 points. The Child-Pugh score is used to determine the Child-Pugh classification (A, B, or C).

Parameter	Child-Pugh Score		
	1	2	3
Total Bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Ascites	Currently with no ascites or ascites only detectable on imaging (grade 1) and not on diuretics	Currently ascites only detectable on imaging (grade 1) and treated with diuretics OR with overt ascites (grade 2 or 3) that is diuretic responsive	Currently with overt ascites (grade 2 or 3) that is not diuretic responsive
Hepatic Encephalopathy (HE)	Currently with no overt HE and not on specific therapy*	Currently with no overt HE and no asterixis on treatment with specific therapy OR currently with grade 2 HE (confused but talking and/or with asterixis) not on treatment with specific therapy	Currently with grade 2 HE despite treatment with specific therapy or currently with grade 3 HE or grade 4 HE
Prothrombin time (sec prolonged) or INR	<4 (INR <1.7)	4-6 (INR 1.7-2.3)	>6 (INR >2.3)

Child-Pugh Classification	Child-Pugh Score
Child-Pugh A	5-6
Child-Pugh B	7-9
Child-Pugh C	10-15

8.2.4 Quality of Life Assessments

Health-related quality of life (QOL) will be assessed by using the Short Form 36 (SF-36) and Chronic Liver Disease Questionnaire (CLDQ).

The SF-36 is a generic, validated, widely used QOL assessment survey that has shown good psychometric properties in diverse disease states, including patients with advanced liver disease. The SF-36 consists of 36 questions that make up 8 subscales (physical function, physical role limitation, bodily pain, general health, vitality, social function, emotional role limitation, and mental health) with 0 as the worst and 100 as the best possible score. An overall physical health score and mental health score are derived from the subscale scores. Norm-based scoring involves a linear transformation to transform scores to a mean of 50 and standard deviation of 10, such that a score >50 is interpreted as better health than the US population, and a score <50 means poorer health. In 713 subjects with NAFLD (61% of whom had definite NASH) enrolled in the NASH Clinical Research Network, those with NAFLD had worse physical and mental health scores compared with the US population with and without chronic illness, and those with NASH had lower physical health compared with NAFLD subjects without NASH [33].

The CLDQ was developed to assess health-related QOL in patients with chronic liver disease [34] and includes 29 questions in 6 domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry. Patients found the CLDQ clear and easy to complete in 10 minutes. The CLDQ correlated with disease severity, showing a gradient between patients without cirrhosis, patients with Child-Pugh A cirrhosis, and patients with Child-Pugh B or C cirrhosis [34]. In a study of 237 patients with chronic liver disease related to NAFLD, chronic HCV, or chronic hepatitis B virus (HBV), NAFLD patients had significantly lower quality of life scores compared to HCV and HBV patients on multiple CLDQ domains [35].

8.2.5 Clinical Outcome Events

Clinical outcome events are an efficacy measure and will be defined based on whether the subject has compensated cirrhosis or decompensated cirrhosis at study entry, and for the latter, depending on what the prior decompensating event was. Subjects may have more than 1 clinical outcome event. Subjects who have compensated cirrhosis on study entry and have a decompensating event could meet criteria for an additional decompensating event(s) if they remain in the study. All clinical outcome events should be reported as AEs. An event reflecting progression of chronic liver disease that meets criteria for being adverse but does not qualify as a clinical outcome event (e.g. worsening ascites not requiring paracentesis) should still be reported as an AE.

Baseline (Day 1) Cirrhosis Stage	Decompensating Event Prior to Day 1	Qualifying Clinical Outcome Events
Compensated	Not applicable	• New onset clinically evident ascites requiring chronic diuretics • Variceal hemorrhage • New onset overt hepatic encephalopathy requiring hospitalization
Decompensated	Ascites, not clinically evident (no ascites or only detectable by ultrasound) on a stable dose of diuretics	• Variceal hemorrhage • Worsening ascites requiring paracentesis • New onset overt hepatic encephalopathy requiring hospitalization
Decompensated	Prior variceal hemorrhage	• Recurrent variceal hemorrhage • New onset clinically evident ascites requiring chronic diuretics • New onset overt hepatic encephalopathy requiring hospitalization
Decompensated	Hepatic encephalopathy, currently with no or mild encephalopathy (Stage 1) on lactulose and/or rifaximin	• Variceal hemorrhage • New onset clinically evident ascites requiring chronic diuretics • Worsening overt hepatic encephalopathy requiring another hospitalization

8.2.6 Liver Metabolic Function by Methacetin Breath Test

The ^{13}C-methacetin breath test (MBT) is a noninvasive tool to assess liver microsomal capacity to metabolize the nonradioactive ^{13}C-labeled Methacetin. The Breath Test System consists of the BreathID® Molecular Correlation Spectrometry (MCS™) device and a test kit containing a breath collection nasal cannula and a nonradioactive isotope ^{13}C-methacetin solution. The BreathID MCS device measures and computes the $^{13}CO_2/^{12}CO_2$ ratio in the subject's exhaled breath in real time. Additional details for the procedure are provided in Appendix II.

The BreathID MCS device is based on an FDA-approved device (510k#: K130524) for assessment of Helicobacter pylori infection in the stomach utilizing ^{13}C-urea as a substrate. As a standalone device, it is classified by the FDA as Class I, which means that for general use, the device is exempt from pre-marketing application. The MBT, which consists of both a device and an unapproved drug component, is however considered an investigational device. Performance and safety of the device utilizing the ^{13}C-methacetin substrate for assessment of liver function have been studied in thousands of subjects worldwide, including in a large US pivotal study (G080107) enrolling over 400 subjects with chronic liver disease from 11 participating sites (including 141 subjects with biopsy proven cirrhosis). This study demonstrated an excellent safety profile of the MBT. Furthermore, there are currently 2 ongoing MBT studies for detection of clinically significant portal hypertension in subjects with advanced liver disease and for assessment of correlation to severity of liver disease in subjects with NAFLD.

Subjects will be asked to sit in a chair with a nasal cannula (a small tube) attached to the BreathID MCS device placed inside their nostrils while breathing normally. The BreathID MCS device will measure the subject's baseline carbon dioxide production for approximately 10 minutes (up to 25 minutes), after which the subject will be administered 1 cup of a solution of a 75 mg Methacetin pre-dissolved in water. Methacetin is exclusively broken up in the liver and turns into carbon dioxide and acetaminophen. The subject will remain sitting in a chair with the nasal cannula in their nose breathing in a normal fashion for another 60 minutes while the BreathID MCS device measures carbon dioxide production. Additional details on the procedure as well as the parameters obtained from the MBT are provided in Appendix II.

The MBT will be performed at select sites at Screening, Week 24, and Week 48. MBT should be performed within 1 week of HVPG but not within 24 hours after HVPG. If MBT is performed on the same day as the HVPG test, it should be performed before the HVPG test. For the Week 24 and Week 48 MBT, subjects should take their morning dose of study drug prior to the test. Sites who elect to participate in the MBT measurements will perform the test at the specified visits for all subjects enrolled at their site.

8.2.7 Liver Stiffness by Transient Elastography (using FibroScan®)

Transient elastography is a non-invasive, reproducible method for measuring liver stiffness that correlates with liver fibrosis and will be measured using FibroScan® (manufacturer Echosens). An ultrasound transducer probe is mounted on the axis of a vibrator; vibrations of mild amplitude and low frequency are transmitted by the transducer, inducing a wave that propagates through the underlying tissue. The propagation velocity of the wave is then measured. The velocity is directly related to tissue stiffness; the stiffer the tissue, the faster the wave propagates. The protocol for the FibroScan® procedure is provided in Appendix III.

Transient elastography measurements will be performed at select sites at Screening, Week 24, and Week 48. Sites who elect to participate in the transient elastography measurements will perform the test at the specified visits for all subjects enrolled at their site.

8.3 LABORATORY TESTS

Blood and urine collected for laboratory tests will be analyzed according to standardized, validated assays. The central laboratory will supply detailed instructions and all necessary containers for blood and urine collections. Blood and urine sample volumes should meet the laboratory's specification.

Table 2 presents the laboratory tests to be performed during the study for screening purposes and safety and efficacy evaluations, including routine chemistry, hematology (complete blood count with automated differential), coagulation, and urinalysis.

Metabolic

Given the significant association of cirrhosis with insulin resistance and components of the metabolic syndrome (especially fasting plasma glucose and blood pressure) [36], particularly for patients with NASH, metabolic parameters will be evaluated in the study including fasting plasma glucose, HbA1c, lipid levels (total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides), and insulin resistance. Insulin resistance will be estimated using a commonly used index based on fasting insulin and glucose called the homeostasis model assessment of insulin resistance (HOMA-IR), which provides a measure of hepatic insulin resistance [37].

Fibrosis Markers

The Enhanced Liver Fibrosis (ELF) panel is based on 3 serum markers (hyaluronic acid [HA], aminoterminal propeptide of type III collagen [P3NP], and tissue inhibitor of matrix metalloproteinase 1 [TIMP-1]) and has demonstrated utility in predicting advanced fibrosis in patients with chronic liver disease related to NAFLD [38], chronic HCV infection [39], and alcoholic liver disease [40]. In addition, a study of 457 patients with chronic liver disease followed for a median of 7 years demonstrated that the ELF test predicted clinical liver-related outcomes [41]. Ferritin is a component of several scores (based on clinical parameters and lab tests) that have demonstrated utility in predicting fibrosis [42]. Lysyl oxidase-like 2 (LOX-L2) is an enzyme expressed in the liver that is responsible for crosslinking collagen and consequently stabilizing it to degradation. LOX-L2 activity is an indicator of fibrosis and has recently demonstrated utility in predicting clinically significant portal hypertension [43].

Table 2. Laboratory Tests

Hematology & Coagulation	Chemistry	Urinalysis	Metabolic	Research	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Neutrophils Eosinophils Monocytes Basophils Lymphocytes MCV, MCH, MCHC, MPV Peripheral smear[1] INR, PT, PTT	BUN, Creatinine, Creatinine clearance (Cockcroft-Gault), Ca, Na, K, Cl, Phosphorus, Mg, Total CO_2 (Bicarbonate), AST[2], ALT[2], Total bilirubin, Direct bilirubin Alkaline phosphatase, Uric acid, Albumin, Total protein, Globulin, LDH, GGT, Glucose serum β-HCG and urine pregnancy test[3] **DILI Confirmation (as needed)** • ALT, AST, Total and direct bilirubin, GGT, alkaline phosphatase, albumin, CBC, INR	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Microscopy[4] Protein[5] (quantitative) Creatinine[5] (quantitative)	Hemoglobin A1c Lipid Panel • Total cholesterol • LDL • HDL • Triglycerides Fasting insulin, HOMA-IR[6]	**Fibrosis Markers** ELF Panel (Hyaluronic acid, P3NP, TIMP-1) Ferritin LOX-L2 **Peripheral and HVPG Biomarkers** Caspase 3/7 cCK18 flCK18 **Population PK including back-up**	**Etiologic screen[7]** • HBsAg • Anti-HCV Ab[8] • Ferritin, transferrin saturation (calculated from iron, TIBC, UIBC) • Ceruloplasmin • ANA • α1-antitrypsin α–fetoprotein[7] Transporter genotyping **DILI Monitoring (as needed)** First visit after confirmation • ALT, AST, Alkaline phosphatase, INR, Total and direct bilirubin, GGT, albumin, CBC • HAV IgM, HBsAg, Anti-HCV antibody[8], HEV IgM, CMV IgM • EBV panel (VCA-IgM, VCA-IgG) • Autoimmune hepatitis (ANA, SMA, anti-LKM1) • Testing for Gilbert's, as needed Additional visits (as needed) ALT, AST, Alkaline phosphatase, INR, Total and direct bilirubin, GGT, albumin, CBC

Abbreviations: ANA=antinuclear antibody; anti-LKM1=anti-liver kidney microsomal type 1 antibody; CBC=complete blood count; CMV=cytomegalovirus; CO_2=carbon dioxide; EBV=Epstein-Barr virus; HAV = hepatitis A virus; HBsAg= hepatitis B surface antigen; HEV=hepatitis E virus; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; MPV=mean platelet volume; PTT=partial thromboplastin time; RBC=red blood cell; SMA=smooth muscle antibody; TIBC=total iron binding capacity; UIBC= unsaturated iron binding capacity; VCA-IgG=viral capsule antigen immunoglobulin G; VCA-IgM=viral capsule antigen immunoglobulin M

1 Lab to complete automatically if necessary
2 A second test for ALT and AST is required during Screening at least 2 weeks from the first draw
3 For females of reproductive potential
4 Only if urine dipstick is positive for blood or protein
5 At Screening and Day 1, with subsequent tests as needed (e.g. for evaluation of hepatorenal syndrome)
6 Calculated by the central laboratory
7 At screening only
8 If positive, Hep C confirmation to be completed

8.3.1 Biomarker Assessments

Peripheral blood samples will be obtained according to the Schedule of Events. The following serum biomarkers will be assessed by the central laboratory: caspase 3/7, cCK18/M30, flCK18/M65. An aliquot will be stored until the end of the study and then tested for microparticles. In addition, effects on biomarkers of mechanism of action and inflammation may be measured.

In addition to collection of peripheral blood samples, 2 blood samples will be collected at the time of the HVPG test: a hepatic vein sample, and a paired systemic sample obtained from the jugular vein. For the HVPG samples, the central laboratory will test caspase 3/7, cCK18/M30, and flCK18/M65. Aliquots from the HVPG samples will be stored until the end of the study and then tested for microparticles, coagulation biomarkers, bacterial translocation biomarkers, and hepatic vasculature function biomarkers. Samples will be destroyed once all analyses are completed.

Samples should be processed for serum and plasma, divided into the central laboratory-specified number of aliquots (including back-ups), and frozen at -70 °C or colder. Samples should be shipped on dry ice to the central laboratory.

8.3.2 Population Pharmacokinetic (PK) Assessment

Samples will be obtained according to the Schedule of Events for population pharmacokinetic assessment. After processing, samples should be equally divided into 2 aliquots and frozen at -70 °C or colder. Samples should be shipped on dry ice to the central laboratory. One aliquot will be forwarded to MicroConstants for analysis, and one will be stored at the central laboratory for re-testing if needed. Samples will be destroyed once all analyses are completed.

8.3.3 OATP Transporter Genotyping

The role of genetic variants of OATP1B1 and OATP1B3 transporters on the hepatic uptake of emricasan and their effect on the pharmacokinetics and pharmacodynamics of emricasan is currently not well understood. Genetic polymorphism(s) can play an important role in the pharmacokinetics and pharmacodynamics of many drugs. If the subject provides consent, a blood sample will be collected on Study Day 1 to evaluate each subject's OATP transporter genetic variants. Samples will be shipped to the central laboratory and then to Gentris for testing. Samples will be destroyed once all analyses are completed.

8.3.4 Blood Volume

The total blood sampling volume for an individual subject is approximately 231 mL for subjects who complete the initial 24-week randomized treatment only and 306 mL for subjects who complete the 48-week randomized treatment, as shown in Table 3.

Table 3. Blood Volume

Sample Type	Sample Volume (mL)	Number of Samples Per Study Phase				24-Week Treatment	48-Week Treatment
			Treatment				
		Screening	Initial 24 Weeks	Continued 24 Weeks	Follow-Up	Total Volume (mL)	Total Volume (mL)
Hematology	2	1	7	3	1	18	24
Chemistry	6	1	7	3	1	54	72
Coagulation	3	1	7	3	1	27	36
Fibrosis markers	8	0	2	1	0	16	24
Lipids[1]	-	0	2	1	0	-	-
Insulin	2	0	2	1	0	4	6
HbA1c	2	0	2	1	0	4	6
Etiologic screen	10	1	0	0	0	10	10
α-fetoprotein	2	1	0	0	0	2	2
Serum pregnancy test[1, 2]	-	1	1	0	0	-	-
Population PK	6	0	6	3	0	36	54
Biomarkers – peripheral blood	4	1	7	3	1	36	48
Biomarkers (plasma) – HVPG samples (hepatic vein, systemic)	4	1	1	0	0	8	8
Biomarkers (serum) – HVPG samples (hepatic vein, systemic)	4	1	1	0	0	8	8
OATP transporter genotyping	6	0	1	0	0	6	6
Second screening liver tests	2	1	0	0	0	2	2
TOTAL						**231**	**306**

1 Drawn as part of chemistry panel
2 For females of reproductive potential only
Note: Additional blood samples may be taken at times specified by the Sponsor or the Investigator (or due to sample/test repeat).

8.4 SPECIFIC STUDY VISIT INFORMATION

The following sections provide specific details of the assessments to be performed at each study visit as noted in the Schedule of Events:

8.4.1 Screening Phase (Week -6 to Day 0)

The following study evaluations will be performed during the course of the Screening phase:

- Signed informed consent
- Eligibility criteria (inclusion and exclusion criteria)
- Medical and surgical history
- Assessment for adverse events, including biliary colic symptoms
- Review of current medications including prescription and nonprescription drugs, vitamins, and dietary supplements
- Comprehensive physical examination including vital signs, height, weight
- Assessment of Child-Pugh clinical features
- 12-lead ECG
- Screening questionnaires for alcohol dependence: AUDIT, Skinner
- Clinical laboratory evaluations: chemistry, hematology, coagulation, urinalysis, etiologic screen, α-fetoprotein, serum pregnancy test (for females of reproductive potential)
    - AST, ALT, and total and direct bilirubin should be measured twice during the screening phase (at least 2 weeks apart)
- Blood sample for biomarkers
- Liver and gallbladder ultrasound
- Esophagogastroduodenoscopy
- HVPG, including collection of hepatic vein and systemic blood samples
- Methacetin breath test (at select sites)
- FibroScan® (at select sites)

In general, the HVPG should be performed after the subject meets all other eligibility criteria. To identify subjects more likely to meet the HVPG ≥ 12 mmHg criteria, it is recommended (but not required) that subjects have one of the following prior to having the HVPG test:

1. History or presence of medium or large varices
2. Evidence of collateral circulation on imaging
3. History of ascites

8.4.2 Double-Blind Phase (Day 1)

- Confirmation of eligibility criteria
- Review concomitant medications and other therapies (vitamins and dietary supplements)
- Assessment for adverse events, including biliary colic symptoms

- Focused physical examination, vital signs, weight, assessment of Child-Pugh clinical features
- Questionnaires: SF-36, Chronic Liver Disease Questionnaire
- Clinical laboratory evaluations (after fasting at least 10 hours): chemistry, hematology, coagulation, urinalysis, metabolic parameters (insulin, lipids, HbA1c), fibrosis markers, serum and urine pregnancy tests (for females of reproductive potential)
- Blood samples for biomarkers and OATP transporter genotyping
- Study drug dispensation

The study procedures specified for Day 1 should be performed prior to dosing with study drug.

8.4.3 Double-Blind Phase (Week 4)

- Review concomitant medications and other therapies (vitamins and dietary supplements)
- Assessment for adverse events, including biliary colic symptoms
- Study drug compliance assessment
- Focused physical examination, vital signs, weight, assessment of Child-Pugh clinical features
- 12-lead ECG
- Clinical laboratory evaluations: chemistry, hematology, coagulation, urinalysis, urine pregnancy test (for females of reproductive potential)
- Blood samples for biomarkers and population PK
- Study drug dispensation

8.4.4 Initial 24-Week Double-Blind Phase (Week 8, Week 12, Week 16, Week 20)

- Review concomitant medications and other therapies (vitamins and dietary supplements)
- Assessment for adverse events, including biliary colic symptoms
- Study drug compliance assessment
- Focused physical examination, vital signs, weight, assessment of Child-Pugh clinical features
- Questionnaire: AUDIT-C (Week 12 only)
- Clinical laboratory evaluations: chemistry, hematology, coagulation, urinalysis, urine pregnancy test (for females of reproductive potential)
- Blood samples for biomarkers and population PK
- Study drug dispensation

8.4.5 Initial 24-Week Double-Blind Phase (Week 24)

- Review concomitant medications and other therapies (vitamins and dietary supplements)
- Assessment for adverse events, including biliary colic symptoms
- Study drug compliance assessment

- Comprehensive physical examination, vital signs, weight, assessment of Child-Pugh clinical features
- 12-lead ECG
- Questionnaires: SF-36, Chronic Liver Disease Questionnaire, AUDIT-C
- Clinical laboratory evaluations (after fasting at least 10 hours): chemistry, hematology, coagulation, urinalysis, fibrosis markers, metabolic parameters (insulin, lipids, HbA1c), urine pregnancy test (for females of reproductive potential)
- Blood samples for biomarkers and population PK
- HVPG, including collection of hepatic vein and systemic blood samples
- Methacetin breath test (at select sites)
- FibroScan® (at select sites)
- Signed informed consent (for subjects who signed consent for the second 24-week treatment phase only)
- Study drug dispensation (for subjects who signed consent for the second 24-week treatment phase only)

8.4.6 Continued 24-Week Double-Blind Phase (Week 32 and Week 40)

- Review concomitant medications and other therapies (vitamins and dietary supplements)
- Assessment for adverse events, including biliary colic symptoms
- Study drug compliance assessment
- Focused physical examination, vital signs, weight, assessment of Child-Pugh clinical features
- Clinical laboratory evaluations: chemistry, hematology, coagulation, urinalysis, urine pregnancy test (for females of reproductive potential)
- Blood samples for biomarkers and population PK
- Study drug dispensation

8.4.7 Continued 24-Week Double-Blind Phase (Week 48)

- Review concomitant medications and other therapies (vitamins and dietary supplements)
- Assessment for adverse events, including biliary colic symptoms
- Study drug compliance assessment
- Comprehensive physical examination, vital signs, weight, assessment of Child-Pugh clinical features
- 12-lead ECG
- Questionnaires: SF-36, Chronic Liver Disease Questionnaire, AUDIT-C
- Clinical laboratory evaluations (after fasting at least 10 hours): chemistry, hematology, coagulation, urinalysis, fibrosis markers, metabolic parameters (insulin, lipids, HbA1c), urine pregnancy test (for females of reproductive potential)
- Blood samples for biomarkers and population PK

- Methacetin breath test (at select sites)
- FibroScan® (at select sites)

8.4.8 Follow-Up Phase (2 weeks after Week 24 or Week 48)

Subjects will be seen approximately 2 weeks after Week 24 or Week 48 (either at Week 26 or Week 50) or early termination. Follow-up procedures will consist of the following:

- Review concomitant medications and other therapies (vitamins and dietary supplements)
- Assessment for adverse events, including biliary colic symptoms
- Focused physical examination, vital signs, weight, assessment of Child-Pugh clinical features
- 12-lead ECG
- Clinical laboratory evaluations: chemistry, hematology, coagulation, urinalysis, urine pregnancy test (for females of reproductive potential)
- Blood sample for biomarkers

8.5 PRIOR AND CONCOMITANT MEDICATIONS

Medications to treat complications of portal hypertension (e.g. non-selective beta blockers, nitrates, diuretics, lactulose, rifaximin, etc.) as well as statins should be maintained at a stable dose during the study if possible but may be adjusted if clinically indicated. Any changes to the dose or use of these medications should be entered on the case report form. Subjects should not take any potentially hepatotoxic drugs, herbal preparations, or supplements during the Screening period and throughout the study.

Subjects should avoid taking new herbal preparations and supplements during the study that are chronically administered unless medically indicated. All prescription and ‘over-the-counter’ medications, including herbal preparations and supplements, taken by the subject at Screening and through to study follow-up will be recorded on the Concomitant Medications case report form. The generic drug name, indication, dose, and dates of drug administration will be recorded. Any additions, deletions, or changes in the dose of these medications should be entered on the case report form. All subjects will be questioned about concomitant medication usage at each study visit. No other investigational medication should be taken during the study except for methacetin as specified in the procedures for the methacetin breath test.

8.6 OTHER PRECAUTIONS AND RESTRICTIONS DURING THE STUDY

Subjects should be contacted prior to each study visit to remind them to take their study drug the night before and the morning of the study visit and to remind them to follow directions for fasting status for the relevant study visits. Subjects should be fasting (except for morning medications including study drug and NSBB which can be taken with water) at least 10 hours before study visits at Day 1, Week 24, and Week 48.

8.7 SUBJECT AND STUDY TERMINATION

8.7.1 Reasons and Procedures for Early Termination

Subjects may be withdrawn from the study at their own request, upon request of the Investigator, or by the Sponsor at any time or for any reason. Reasons for removing a subject from the study may include:

- subject withdrawal of consent;
- Investigator decision (Investigator feels it is in the subject's best interest to terminate participation)
- the subject develops an AE necessitating withdrawal
- subject non-compliance with study drug and/or study procedures
- subject lost to follow-up
- major protocol violation
- death
- the study is terminated by the Sponsor
- other reasons (e.g. subject requires an unacceptable concomitant medication, or pregnancy in a female study subject)

If a subject is lost to follow-up (i.e., fails to return for study visits), reasonable efforts should be made to contact the subject and complete study termination procedures. Efforts and means used to contact the subject should be recorded in the source documents.

All subjects who discontinue the study because of AEs will be followed up at suitable intervals in order to evaluate the course of the AE and to ensure the reversibility or stabilization of the abnormality.

All subjects who prematurely discontinue the study, regardless of the cause, should have an Early Termination visit scheduled as soon as possible after the discontinuation date. For subjects who prematurely discontinue before Week 24, assessments scheduled at the Week 24 visit should be performed, and for subjects who prematurely discontinue after Week 24, assessments scheduled at the Week 48 visit should be performed (see Appendix I, Schedule of Events). Study drug should be continued (unless the subject is discontinuing treatment due to an adverse event) until the Early Termination visit is performed. A follow-up visit should then be scheduled to occur approximately 2 weeks following the Early Termination visit.

8.7.2 Withdrawal from Study Drug Treatment but Not from Study Participation

All efforts should be made to encourage subjects to continue participation in the study including undergoing all protocol-specified assessments even if they discontinue study drug treatment, unless they withdraw consent for participating in the study, are lost to follow-up, undergo liver transplantation, or the investigator deems that it is not in the best interest of the subject to continue participating in the study or becomes unblinded to study drug assignment. Subjects who meet criteria for withdrawal of study drug due to progression to Child-Pugh C or who develop a new or worsening decompensation event should continue participation in the study,

even if withdrawn from study drug. Discontinuation of study drug should be documented in the database.

8.7.3 Termination of the Study

Participation in the study by an Investigator may be terminated prematurely with sufficient notice in advance by the Investigator for any reason as per the terms of the contract with the Sponsor. The reason should be communicated in writing to the Sponsor.

The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons. Such a termination must be implemented by the Investigator, if instructed to do so by the Sponsor, in a time frame that is compatible with the subjects' well-being.

9 INVESTIGATIONAL MEDICINAL PRODUCT

For the purpose of this protocol, the term 'investigational medicinal product (IMP)' is interchangeable with the term 'study medication' and/or 'study drug'.

All study medication (emricasan [IDN-6556] and matching placebo) will be manufactured according to Good Manufacturing Practice (GMP).

9.1 EMRICASAN AND PLACEBO SUPPLIES

The double-blind supplies of emricasan will be in bottles containing 60 capsules of emricasan (5, 25, or 50 mg). Placebo will also be supplied in bottles containing 60 capsules. Each bottle will contain sufficient supply to dose subjects for four weeks.

At the investigational site, emricasan and placebo supplies must be stored in a secure, lockable area. Excursions that are outside of the 15-30 °C (59 to 86 °F) range will need to be reported.

Subjects should be instructed to store their study drug bottles with the caps tightly closed in a safe area at room temperature (15-30 °C [59 to 86 °F]). Study drug bottles should not be stored near heating devices, at high temperatures or humidity, or where children or pets have access to them.

9.2 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

The packaging and labeling of study medication supplies will be performed according to GMP standards by a designated qualified vendor.

Emricasan and placebo capsules will be dispensed to subjects in the provided bottles in sufficient quantities for continuation of treatment to at least the next scheduled visit, along with instructions for the proper method of taking the study drugs.

All study drug bottles will carry a uniquely numbered label that will also contain the drug description and conditions for storage.

9.3 INVESTIGATIONAL MEDICINAL PRODUCT DISPENSING AND ACCOUNTABILITY

All study drugs must be dispensed in the original containers provided by either the Sponsor or the drug manufacturer in order to assure stability of the drugs. At each visit, subjects must be instructed to return all unused capsules in partially or completely full bottles in order to adequately assess each subject's compliance with dosing instructions. The number of capsules remaining in each bottle should be counted at each visit to assess subject compliance with study drug administration. Also, except at the last dispensing visit, every bottle containing capsules should be re-dispensed to subjects, and subjects should be instructed to finish all capsules in each bottle before opening a new bottle. At the end of the study, all unused capsules and all dispensed bottles (used, unused, or empty) must be returned by every subject for accounting.

9.4 INVESTIGATIONAL MEDICINAL PRODUCT ADMINISTRATION

Subjects will be instructed to take emricasan or placebo twice daily about the same time in the morning and evening without regard for food. All study procedures specified at Day 1 should be performed prior to administration of the first dose of the investigational medicinal product.

10 WARNINGS AND PRECAUTIONS

10.1 TERATOGENICITY AND FERTILITY

Teratology studies conducted in rats and rabbits demonstrated that emricasan was teratogenic. There have been no studies with this compound in pregnant women, but based on the preclinical findings, emricasan has the potential to be teratogenic (refer to the Investigator's Brochure for further details). Therefore, emricasan should not be used in pregnant women or women planning to become pregnant.

Emricasan has also been found to reduce male and female fertility in rats. There have been no studies on the effect of emricasan on fertility in men and women, but based on the preclinical findings, emricasan has the potential to reduce fertility in humans.

10.2 CONTRACEPTION FOR FEMALE SUBJECTS OF REPRODUCTIVE POTENTIAL

For the purposes of this study, females of reproductive potential are defined as any female who has experienced menarche and does not meet one of the following conditions:

- Postmenopausal
- Permanently sterile (i.e,. due to hysterectomy, bilateral salpingectomy or bilateral oophorectomy)
    - Tubal ligation is not considered to be a permanent sterilization method

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone [44] level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement in the post-menopausal range is not sufficient for a subject to be considered post-menopausal.

Females of reproductive potential must undergo or adhere to the following procedures during the screening, treatment, and follow-up periods of the study to help ensure that they are not pregnant prior to starting treatment with study medication as well as to minimize exposure of the fetus to study medication should an unintentional pregnancy occur:

- Serum pregnancy test at first screening visit (up to 6 weeks prior to Day 1)
- Serum and urine pregnancy test at Day 1
    - Urine pregnancy test result should be confirmed negative before first dose of study drug is administered
    - A serum pregnancy test may detect a very early pregnancy approximately 1 week before a urine pregnancy test is positive. Subjects should be contacted as soon as possible if the serum pregnancy test is positive.
- Urine pregnancy test at all study visits after Day 1
- Urine pregnancy test should be obtained in the event of a missed period by >7 days OR if unusual menstrual bleeding occurs
- Use effective contraception for at least 4 weeks prior to Day 1 and continuing for at least 4 weeks after the last dose of study drug

Females of reproductive potential are strongly encouraged to use at least one of the following highly effective methods of contraception [45]:

- Complete sexual abstinence during the entire duration of the study including the follow-up period
- Intrauterine device or intrauterine hormone-releasing system, which has been shown to have a failure rate <1% within the first year of use under "typical use" conditions
- Bilateral tubal ligation or occlusion
- Partner who had vasectomy at least 3 months prior to Screening (only if the partner is the sole sexual partner)

If one of the above highly effective methods of contraception is not used, females of reproductive potential must use 2 forms of contraception (1 from each of the following 2 categories):

For subjects with compensated cirrhosis:

1. combined (estrogen and progestogen containing) hormonal contraceptive (oral, transdermal, or vaginal) *or* oral/injectable/implantable progestogen-only hormonal contraception AND
2. barrier method such as a) male or female condom (with or without spermicide); b) cap, diaphragm, or sponge with spermicide

For subjects with decompensated cirrhosis:

1. oral/injectable/implantable progestogen-only hormonal contraception AND
2. barrier method such as a) male or female condom (with or without spermicide); b) cap, diaphragm, or sponge with spermicide

Notes:

a) Combined oral contraceptives are considered medical eligibility criteria Category 4 ("A condition that represents an unacceptable health risk…") in patients with decompensated cirrhosis [46]. Combined oral contraceptives containing estrogens may therefore not be used in decompensated study subjects.

b) Progestogen-only hormonal contraception, including levonorgestrel-releasing IUDs, is considered to be Category 3 ("A condition for which the theoretical or proven risks usually outweigh the advantages…") when used in patients with decompensated cirrhosis [46]. If possible, a single highly effective method of contraception should be used in decompensated subjects. However, the risk/benefit of progestogen contraception may be more favorable than usual in a decompensated subject treated with emricasan who cannot or will not use a single highly effective method of contraception, since emricasan is a potentially teratogenic drug.

If pregnancy occurs in a female subject taking study drug, the subject should be instructed to immediately stop taking the study drug, and the Investigator should inform the Sponsor within 24 hours of the Investigator's learning of the pregnancy. If the female subject is in the

double-blind phase of the study, the treatment arm may be unblinded (after discussion between the Investigator and the Medical Monitor). If pregnancy occurs in a female subject after the double-blind phase of the study but within 4 weeks of taking study drug, the Investigator should inform the Sponsor immediately.

If the female subject chooses to terminate the pregnancy, the Investigator should document the termination and contact the Medical Monitor to discuss whether continued participation of the subject in the study is appropriate. If the female subject chooses to continue the pregnancy, the procedures for withdrawing a subject from the study should be completed, and the Investigator should attempt to obtain information on the outcome of the pregnancy. If the pregnancy goes to term, then the Investigator should also attempt to obtain information on the health of the infant after delivery and provide the information to the Sponsor.

10.3 CONTRACEPTION FOR MALE SUBJECTS WITH FEMALE PARTNERS OF REPRODUCTIVE POTENTIAL

All males, even those who are permanently sterile through bilateral orchiectomy, should use a latex or synthetic condom during any sexual contact while on study drug treatment and for 4 weeks after the last dose of study medication.

If pregnancy occurs in the female partner of a male subject during the double-blind phase of the study or within 4 weeks of taking study drug, the Investigator should inform the Sponsor immediately. The progress of the pregnancy in a male subject's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested for the infant. Follow-up will be performed to the extent permitted.

10.4 USE OF ESTROGENS IN SUBJECTS WITH DECOMPENSATED CIRRHOSIS

Estrogens have the potential to cause drug-induced liver injury (DILI) in patients with decompensated cirrhosis, and many estrogen product labels carry warnings or precautions for that patient population. There are alternatives to estrogen-based contraceptives that are acceptable in decompensated cirrhosis; therefore estrogen-containing contraceptives should not be used for decompensated subjects in this study.

Due to the risk of drug-induced liver injury, it is strongly recommended that estrogens not be used as hormone replacement therapy for subjects in this trial. However, there may not be good alternatives to estrogens for the treatment of severe post-menopausal (estrogen-withdrawal) symptoms. If the Investigator and subject agree that the potential risk of liver injury is outweighed by other benefits in that particular subject, estrogens may be cautiously used. In that case, the lowest estrogen dose that results in adequate control of the most severe symptoms should be used.

11 DOCUMENTATION OF DATA

11.1 SOURCE DOCUMENTATION

Source data is all information in original records and certified copies of original records of clinical findings, observations and other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents are any original document, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, any electronic medical record). The clinical site study staff members will record the source data in their medical charts, except for data that are available on original printouts or as data files.

All clinical work conducted under this protocol will be conducted according to GCP guidelines. This includes an inspection by the Sponsor and/or health authority representatives at any time. The Investigator will agree to the inspection of study-related records by health authority representatives and/or the Sponsor. If the study is to be audited by a health authority at a given site, the Investigator will agree to immediately notify the Sponsor upon receipt of the audit notification.

11.2 DATA ENTRY IN DATABASE

All data will be entered electronically by the study personnel using a validated Electronic Data Capture [47] database specifically designed for this study.

11.3 QUERY CHECKS

The raw data will be checked by appropriate programs for consistency and plausibility according to previously defined query checks documented in a data validation plan.

11.4 CODING OF ADVERSE EVENTS, DRUGS, AND DISEASES

After data entry, the AEs will be coded according to the MedDRA (Medical Dictionary for Regulatory Activities) dictionary. Concomitant medications will be coded according to the World Health Organization Drug Reference List.

11.5 STUDY LANGUAGE AND TRANSLATIONS

The primary study materials (protocol, correspondence, clinical study report) will be prepared in English. However, where the first language of the subject, study personnel, or others involved in the study (such as Ethics Committees) is not English, appropriate arrangements will be made to have translations of the documents in the local language, as necessary. In any case, a qualified translator will need to provide documentation to attest to the fact that the foreign language document is an accurate reflection of the respective English language document. Any subject facing documents including the subject informed consent will also need to be translated and back translated by a qualified translator.

Additional documents may need to be translated into English (e.g., transcripts of necessary additional hospital tests that may occur), and others (e.g., new safety information) may need to be translated into the local language. The Sponsor, or designee, will make arrangements for such translations to occur promptly.

12 STATISTICAL METHODS

12.1 INTRODUCTION

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the Sponsor. Should any of the assumptions of the statistical methods described below not be met, alternative methods will be applied and documented in the Clinical Study Report.

12.2 PARAMETERS OF INTEREST

12.2.1 Safety Variables

The following variables will be recorded for the safety evaluation:

- Adverse events
- Vital signs, weight, physical examination
- Laboratory tests (e.g. chemistry, hematology, coagulation, urinalysis)
- ECGs
- Liver and gallbladder events and ultrasound

12.2.2 Efficacy Variables

The following variables will be recorded for the efficacy evaluation:

Primary

- HVPG mean change from baseline at Week 24

Secondary

- HVPG response (based on 20% reduction from baseline) at Week 24
- Caspase 3/7 and ALT at Weeks 24 and 48

Exploratory

- HVPG response (based on 10% reduction from baseline) at Week 24
- MELD and Child-Pugh scores, regression, and progression at Weeks 24 and 48
- cCK18/M30, flCK18/M65, AST, total bilirubin, INR, and albumin at Weeks 24 and 48
- Fibrosis markers at Weeks 24 and 48
- Health-related quality of life, as measured by SF-36 and CLDQ, at Weeks 24 and 48
- Clinical outcomes (development of decompensation or worsening of decompensation) at Weeks 24 and 48
- Liver metabolic function assessed by methacetin breath test (at select sites) at Weeks 24 and 48
- Liver stiffness by transient elastography (at select sites) at Weeks 24 and 48

12.3 ANALYSIS POPULATIONS

The Enrolled population will consist of all subjects who signed an informed consent form.

The Full Analysis Set (FAS) consists of all randomized subjects who have received at least one dose of study drug. The analyses based on the FAS will be conducted on an intention-to-treat principle (i.e., all subjects will be analyzed with the group to which they were randomly assigned).

The Per Protocol Set (PPS) consists of all subjects in the FAS who do not have any significant protocol deviations.

The Safety Analysis Set consists of all subjects randomized and have received at least one dose of study drug on an "as treated" basis (i.e., all subjects will be analyzed by the treatment they have taken).

All efficacy analyses will be based on the FAS, with the primary analysis also being conducted using the PPS. All safety analyses will be based on the Safety Analysis Set.

12.4 SAMPLE SIZE

It is planned to enroll subjects into this study in order to randomize 240 subjects (60 subjects per group) to receive 1 of 3 treatment groups of emricasan or placebo. Subjects will be randomly assigned to received either emricasan 50 mg BID, emricasan 25 mg BID, emricasan 5 mg BID, or matching placebo in a 1:1:1:1 ratio. Assuming a 20% attrition rate, it is expected that approximately 192 subjects (48 subjects per group) will have a Week 24 HVPG assessment.

This sample size will provide 81% power to detect a statistically significant difference between at least 1 emricasan treatment group and placebo in the mean change from baseline in HVPG. This calculation assumes a mean difference between an active treatment group and placebo of 3 mmHg and a sample standard deviation of 4.5 mm Hg. This calculation also applied a Dunnett's adjustment of comparing 3 active treatment groups with placebo.

The assumptions for the shape of the dose response was based on modelling of cCK18/M30 data in HCV patients where the estimated ED50 was 1 mg total daily dose. Based on data in the literature and discussion with key experts in the field, a clinically meaningful difference in the change from baseline in HVPG is approximately 2.5 - 3 mmHg, depending on the baseline value. Subjects in Study IDN-6556-11 (open-label pilot study evaluating the effect of emricasan on HVPG for 28 days) with a baseline HVPG ≥12mmHg had a sample standard deviation of 4.05 mmHg.

12.5 STATISTICAL ANALYSES

12.5.1 General

All parameters will be analyzed using descriptive methods. Continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum, maximum). Summary statistics for categorical variables will include number of observations and percentages.

Analyses will be done using the validated statistical software of SAS® (version 9.3 or later).

12.5.2 Safety Analysis

Safety will be assessed by treatment compliance, treatment exposure, adverse events, gallbladder monitoring, potential DILI, laboratory tests, vital signs, physical examinations, ECGs, and prior/concomitant medications. All safety assessments will be summarized descriptively.

AEs will be tabulated by system organ class and preferred term. Summary of AEs by severity and relationship to treatment will also be provided.

Change from baseline in laboratory parameters and vital signs will also be summarized descriptively. Abnormal laboratory and ECG findings will be tabulated against appropriate cut-off points using frequency counts and percentages. Any prior and concomitant medications will be described.

12.5.3 Efficacy Analysis

Primary Endpoint: Mean Change from Baseline at Week 24 in HVPG

The primary endpoint for this study is the change from baseline (CFB) at Week 24 in HVPG. The change from baseline will be calculated as HVPG at Week 24 minus HVPG at baseline (HVPGW24-HVPGBL). Hence, a negative value will represent a decrease in HVPG at Week 24.

Absolute and CFB values for the primary endpoint will be summarized descriptively by treatment group. Comparisons of the mean CFB in HVPG at Week 24 between each emricasan treatment group and placebo will be analyzed using a fixed effects Analysis of Covariance (ANCOVA) model using the FAS. This model will include the treatment group, compensated vs. decompensated status, and NSBB use as fixed effects with baseline HVPG as a covariate. Least-square adjusted means (LSMeans) for each treatment group will be reported, along with the estimated difference in LSMeans and corresponding 95% confidence intervals (CIs). A Dunnett's test will be applied to adjust for the multiple comparisons of each emricasan treatment group with placebo.

Missing data for the primary endpoint will be imputed using a multiple imputation technique as described in Section 14 of the SAP. Sensitivity analyses of the primary endpoint will be conducted using the following:

- Repeat the primary analysis using observed cases
- Repeat the primary analysis using the PPS
- Tipping point analysis assessing impact of missing data

Secondary Endpoints

All secondary analyses will be conducted using the FAS. No multiplicity adjustments will be applied within or across analyses of secondary endpoints.

The dose response of emricasan on portal pressure as assess by HVPG will be characterized using a plot of the CFB at Week 24 in HVPG across treatment group. Treatment groups will be ordered as placebo, emricasan 5 mg BID, emricasan 25 mg BID, and emricasan 50 mg BID.

Absolute and CFB at each visit in Caspase 3/7 and ALT will be summarized descriptively by treatment group and visit. Treatment comparisons for CFB at Weeks 24 and 48 in Caspase 3/7 and ALT will be conducted using a similar ANCOVA model as described for the primary analysis, using the appropriate baseline value.

If the CFB at each visit in caspase 3/7 and ALT is deemed to be transformed, the geometric mean will also be provided. In this scenario, the relative change from baseline at Weeks 24 and 48 will be calculated for caspase 3/7 and ALT by back transforming the change from baseline in log-transformed data.

Exploratory Endpoints

All exploratory endpoints will be summarized descriptively by treatment group and visit. Treatment comparisons for continuous endpoints will be conducted at Weeks 24 and 48 in a similar ANCOVA model as the primary analysis, using the appropriate baseline value. Treatment comparisons for response, regression, and progression endpoints will be analyzed using a logistic regression model using treatment group, compensated vs. decompensated status, and NSBB use as fixed effects and the appropriate baseline value as a covariate. Adjusted odds and risk ratios for each comparison of emricasan with placebo will be provided along with the corresponding 95% CI.

Safety Endpoints

All safety endpoints will be summarized descriptively by treatment group.

12.5.4 Timing of Analyses

After the last subject completes their Week 24 visit, all data for all subjects across all visits will be cleaned, locked, and considered as the main analysis for this study. This Week 24 analysis will include all primary, secondary, and exploratory endpoint analyses. Although the Sponsor will be unblinded for the Week 24 analysis, the investigative sites will remain blinded throughout the study. The purpose of the Week 24 analysis is internal decision making.

The final analysis of the study (i.e., Week 48 analysis) will be conducted after all subjects have completed all study visits up to and including the follow-up visit. All study data across all subjects and visits will be cleaned and locked for this final analysis.

12.6 HANDLING OF MISSING DATA

Missing data for the primary endpoint will be imputed using a multiple imputation analysis, assuming that the missing data pattern is missing at random. The pattern and amount of missing data pattern will be assessed to determine the number of imputed datasets to be derived for the multiple imputation analysis. The SAS multiple imputation procedure will be used to generate multiply imputed datasets (roughly the percent attrition seen in the study), with each multiply imputed dataset being analyzed as described for the primary endpoint analysis. The results for each imputed dataset analysis will then be summarized using the SAS MIANALYZE procedure with the appropriate statistics to be reported.

Imputed values will be dependent on examination of treatment group and potential risk factors, such as age, gender, compensated/decompensated status, use of NSBB, baseline MELD

score, and baseline C-P classification. A monotone regression method will be applied to impute missing CFB at Week 24 HVPG values.

An LOCF method will also be applied to the primary endpoint in the cases where an HVPG measurement is provided prior to Week 24.

No imputation methods will be applied for secondary or exploratory efficacy and all safety endpoints.

12.7 DATA MONITORING COMMITTEE (DMC)

An independent DMC will review unblinded safety data from this study approximately every three months. Members of the DMC will not be allowed to participate as Investigators in this study and will not otherwise consult for the Sponsor.

A charter, which will include a detailed description of the scope and the extent of its responsibilities and procedures, will be implemented prior to any data review. These documents (charter, open and closed meeting minutes, etc.) will be considered part of the study documentation, but not of this protocol. The DMC will review data within its general remit to oversee subject safety in the study, and provide recommendations and guidance to the Sponsor in accordance with the procedures stated in its charter.

All Investigators, responsible IRB/IECs, and applicable regulatory agencies will be informed of any decisions made by the Sponsor based on recommendations from the DMC relating to subject safety that affect the conduct of this study. The Investigators will inform the subjects of such actions, and the protocol and ICF will be revised, as appropriate.

13 SAFETY MONITORING AND REPORTING

13.1 ADVERSE EVENT REPORTING OBLIGATIONS

The Investigator is responsible for recording adverse events observed during the study. In addition, certain adverse events (as described in Section 13.2 below) are classified as "serious" and must be reported within 24 hours to Conatus or its designee.

In the case of certain adverse events, the Investigator and the Medical Monitor, after discussing the details of the adverse events, may decide to temporarily interrupt dosing or permanently discontinue study drug treatment in a subset of subjects or in entirety.

13.2 ADVERSE EVENT DEFINITIONS

The following definitions of terms are guided by the ICH and 21 CFR 312.32 and are included herein.

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered study drug related.

Adverse events include, but are not limited to:

- Any symptom or condition not previously reported by the subject (medical history).
- An exacerbation of a pre-existing symptom or condition.
- A significant increase in frequency or intensity of a pre-existing episodic event or condition.
- A drug interaction.
- A condition first detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.

An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or blood transfusion); the condition that leads to the procedure is an adverse event (e.g., bleeding esophageal varices, dental caries).
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

An adverse reaction is any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious 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. 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.

Hospitalizations that fulfill the serious criterion are generally greater than 24 hours in duration. The Investigator should use appropriate medical judgment to determine if a hospitalization less than 24 hours in duration should be considered serious.

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered serious, even if the subject is hospitalized, as long as the study site documents all of the following:

- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject’s consent to participate in the study and the scheduled procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An adverse event or suspected adverse reaction is considered ‘unexpected’ if it is not listed in the Investigator Brochure (or reference safety information) or is not listed at the specificity or severity that has been observed.

The adverse events and their time-adjusted incidence rates in Table 4 are considered anticipated events in patients with cirrhosis and portal hypertension (the study protocol population) and will not be individually reported in an expedited fashion by the Sponsor. The

Investigator is still obligated to report all SAEs whether considered anticipated or not. The severity of these events may be up to severe.

Table 4. Time-Adjusted Incidence Rate for Anticipated Events in Patient Population

Preferred Term	Time Adjusted Incidence Rate (per patient-year)	Preferred Term	Time Adjusted Incidence Rate (per patient-year)
Ascites	0.121	Lobar pneumonia	0.016
Hepatic encephalopathy	0.121	Pleural effusion	0.016
Hepatic failure	0.067	Bacteremia	0.012
Cellulitis	0.052	Biliary cirrhosis primary	0.012
Hepatic cirrhosis	0.052	Dehydration	0.012
Renal failure acute	0.052	Dyspnea	0.012
Hyperkalemia	0.032	Gastroenteritis	0.012
Hyponatremia	0.032	Hydrothorax	0.012
Pneumonia	0.032	Mental impairment	0.012
Urinary tract infection	0.032	Respiratory failure	0.012
Hepatorenal syndrome	0.030	Septic shock	0.012
Oesophageal varices haemorrhage	0.030	Dizziness	0.008
Hepatic neoplasm malignant	0.028	Hypoglycemia	0.008
Peritonitis bacterial	0.028	Liver transplant rejection	0.008
Clostridium colitis	0.020	Metabolic encephalopathy	0.008
Hyperglycemia	0.020	Syncope	0.008
Renal failure	0.020	Hypotension	0.004

There are no anticipated AEs with methacetin.

The Sponsor will determine if a SUSAR or SAE meets the criteria of being reportable as a 7-day or a 15-day safety report.

13.2.1 Pre-Treatment-Emergent Adverse Events

The Sponsor considers adverse events that occur between the time that the subject signs the informed consent form for the study and the time when that subject is first administered the study drugs as “pre-treatment-emergent” events. The start date (and time if necessary) of any adverse events that occur between signing of the informed consent form and the first dose of study drug should be recorded to allow correct classification of these adverse events as pre-treatment-emergent.

13.2.2 Laboratory Abnormalities as Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported adverse event describing a clinical syndrome (e.g., elevated blood urine nitrogen [BUN] and creatinine in the setting of an adverse event of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (e.g., elevated creatinine in a setting of renal failure) should not be recorded as an adverse event. However, isolated laboratory abnormalities should be reported as adverse events if they are considered adverse by the Investigator. Criteria for an adverse laboratory abnormality in this study include:

1. A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension or discontinuation), or
2. A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy), or
3. Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion).

13.3 SEVERITY OF ADVERSE EVENTS

The Investigator must categorize the severity of each adverse event according to the following guidelines:

Mild: Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of study drug administration; and/or not needing therapeutic intervention.

Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of study drug administration; and/or requiring therapeutic intervention.

Severe: Associated with inability of subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

13.4 CLASSIFICATION OF ADVERSE EVENTS BY RELATIONSHIP TO STUDY DRUG ADMINISTRATION

The Investigator must determine whether each adverse event is related to study drug (emricasan or placebo) and whether each adverse event is related to methacetin (investigational drug for the methacetin breath test). The relationship of each adverse event will be assessed by the Investigator after careful consideration, and according to the following guidelines:

Definitely: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered.

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

Possibly: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, but that could reasonably have been produced by a number of other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.

Unlikely: A reaction that does not follow a reasonable temporal sequence from administration, and/or that can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatments.

Not Related: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

For the purposes of regulatory reporting, AEs assessed as definitely, probably, and possibly related are considered related to study drug.

13.5 RECORDING AND REPORTING ADVERSE EVENTS

13.5.1 Recording Adverse Events

All adverse events will be recorded in the appropriate section of the case report form. AEs (except SAEs, see Section 13.8) should be collected for a subject starting from signing of the informed consent until the subject's last study visit (follow-up visit, early termination, or last regularly scheduled study visit). Subjects withdrawn from the study due to adverse events will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided. The Investigator should always group signs and symptoms into a single term that constitutes a single unifying diagnosis if possible.

If the adverse event meets the definition of a serious adverse event, or if the Investigator becomes aware of an unexpected adverse event that places the subject at risk or a pregnancy at any time after the study drug administration up to the end of the study follow-up period, the event must be documented and reported as described in Section 13.5.2.

13.5.2 Investigator Reporting of a Serious Adverse Event

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for prompt notification of serious adverse events to the Sponsor or designee in the EDC of the study and at the contact listed below.

Contact

SynteractHCR Safety Safety Fax: +1-760-268-6500 safetyfax@synteracthcr.com	OR if not available	Mason Yamashita, MD VP, Pharmacovigilance Office: +1-858 376 2617 Mobile: +1-619 306 2125 myamashita@conatuspharma.com

All serious adverse events must be reported to the Sponsor or designee within 24 hours after the Investigator recognizes/classifies the event as a serious adverse event. The following information should be provided at the time of the initial report: subject number, a description of the event, the Investigator judgment of study drug causality, at least one criterion classifying the event as serious, and the name and title of the reporting individual.

After the initial report, as necessary, the Investigator will provide follow-up information on a serious adverse event to the Sponsor or designee within 24 hours after he/she receives that information. Examples of follow-up information include hospital records, case reports, autopsy reports, and other pertinent documents.

The Sponsor will consider the Investigator's assessment of the causality; however, since the Sponsor will assess the overall safety of the study medication, the Sponsor's causality assessment will take precedence, unless the Investigator's assessment must take precedence per country-specific regulations.

13.6 ADDITIONAL INVESTIGATOR RESPONSIBILITIES ON FOLLOW-UP OF SERIOUS ADVERSE EVENTS

The Investigator and supporting personnel responsible for subject care should discuss with the Medical Monitor any need for supplemental investigations of serious adverse events. The results of these additional assessments conducted must be reported to the Sponsor. If a subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to the Sponsor.

13.7 FOLLOW-UP OF ADVERSE EVENTS

All SAEs must be followed until the event resolves, the condition stabilizes, 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 the nature and/or causality of the adverse event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

All non-serious adverse events must be followed until the final study visit, at which point the status of the event (e.g. ongoing, stabilized, resolved) should be documented on the case report form, with date of resolution if the event is resolved.

13.8 NOTIFICATION OF POST-STUDY SERIOUS ADVERSE EVENTS

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigator becomes aware of a serious adverse event, he/she should notify the Sponsor if such an event is attributable to study drug. The notification to the Sponsor of a post-study serious adverse event by the Investigator should occur within 24 hours of becoming aware of the serious adverse event.

13.9 IRB/IEC NOTIFICATION OF SERIOUS ADVERSE EVENTS

The Investigator is responsible for promptly notifying her/his IRB/IEC of all serious adverse events, including any follow-up information, occurring at her/his site. In addition, the Investigator is responsible for submitting information on SUSARs/SAEs received from the Sponsor to her/his local IRB/IEC. However, in some countries, the notification of SUSARs/SAEs to the IRB/IEC will be the responsibility of the Sponsor or Sponsor's designee. Documentation of the submissions to IRB/IEC must be retained in the appropriate study file(s).

13.10 HEALTH AUTHORITY SAFETY REPORTS

The Sponsor or its representatives will submit a safety report to the US Food and Drug Administration (FDA) and any other appropriate regulatory agencies in accordance with country specific requirements, for any serious adverse event that is unexpected and related to the study drug within the appropriate time frame. The Sponsor or its representatives will send copies of each safety report submitted to the FDA and other regulatory agencies to the Investigators who are actively participating in Sponsor clinical studies. Safety reports must be submitted to the appropriate IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC must be retained for each safety report. As instructed by the Sponsor or its designee, safety reports should be retained in the appropriate study files or with the Investigator's Brochure.

14 ADMINISTRATIVE ASPECTS

14.1 INVESTIGATOR RESPONSIBILITIES FOR GENERAL STUDY CONDUCT

It is the Investigator's responsibility to ensure that:

- The protocol, subject information sheet, proposed informed consent form, trial participation card (if applicable), or any information to the Primary Care Physician and any advertisement for subject recruitment are reviewed and approved by the appropriate IRB/IEC, prior to the start of the study.
- The proposed subject information sheet, informed consent form, trial participation card (if applicable) and any proposed advertisement are agreed to by the Sponsor.
- A copy of the IRB/IEC approval letter for the protocol, any amendments, the subject information sheet, the informed consent form, the trial participation card (if applicable) and any advertisements are supplied to the Sponsor prior to starting the study.
- During the course of the study, at intervals not exceeding one year, timely and accurate reports are submitted to the IRB/IEC on the progress of the study and any other local IRB/IEC regulations regarding reporting are satisfied.
- Copies of all reports to and correspondence with and from the IRB/IEC are provided to the Sponsor.
- At the completion or early termination of the study, a final report is made to the IRB/IEC within the applicable IRB/IEC time frames.
- Any significant deviation in the study protocol or any change that may alter subject risk is approved by the Sponsor (and FDA/other regulatory agency review and/or approval is obtained if required) and is approved in writing by the IRB/IEC prior to implementation. All protocol amendments will be submitted to the IRB/IEC.
- Receipt of administrative amendments provided for information only are acknowledged.
- An approval/favorable opinion is obtained from the IRB/IEC on substantial amendments prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants.
- A written notice of approval from the Sponsor is obtained prior to initiating changes to the study protocol.

14.2 PROTOCOL DEVIATIONS

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol violation or deviation to the IRB/IEC, Conatus, and to the regulatory authorities, if required.

14.3 SUBJECT INFORMATION AND CONSENT

Prior to participation in any study-specific procedures, the subject must sign an IRB/IEC-approved written Informed Consent Form in his/her native language (note: all references to "subject" in this section refers to the study subject or his/her legally acceptable representative). The approved written informed consent must adhere to all applicable laws in regards to the safety and confidentiality of the subjects. To obtain and document informed consent, the Investigator should comply with applicable regulations and adhere to ICH GCP standards and the ethical principles in the Declaration of Helsinki (October 2008).

The language in the written information about the study should be as non-technical as practical and should be understandable to the subject. Before informed consent is obtained, the Investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written Informed Consent Form should be signed and personally dated by the subject and the person who conducted the informed consent discussion, with any additional signatures obtained as required by applicable local regulations and IRB/IEC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All subjects will receive a copy of the signed and dated Informed Consent Form.

14.4 SUBJECT CONFIDENTIALITY AND DATA PROTECTION

The processing of personal data in pursuit of this study will be limited to those data that are reasonably necessary to investigate the utility of the study medications used in this study. These data will be processed with adequate precautions to ensure confidentiality according to local laws.

The Sponsor ensures that the personal data are:

- collected for a specified and legitimate purpose
- processed fairly and lawfully
- accurate and up to date

Explicit consent for the processing of personal data will be obtained prospectively from the participating subject. The Sponsor and/or designees whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. This confidentiality will be maintained throughout the complete data processing. Study subjects will be entitled to request confirmation of the existence of personal data held by the Sponsor and will have the right to rectify erroneous or inaccurate data prior to database lock.

14.5 LABORATORY ACCREDITATION

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations in that state and/or country. Reference values and/or normal ranges for the test results must be provided to the Sponsor. The Sponsor must be notified promptly in writing of any reference value changes during the course of the study.

This protocol will analyze pharmacokinetics of emricasan and exploratory serum biomarkers of caspase activity. As such, some of the analytes may be tested at a non-accredited research or analytical laboratory. The requirement for adequate licensure or accreditation will not apply to any research or analytical laboratories utilized in this protocol.

14.6 REQUIRED DOCUMENTS

The Investigator and affiliated institution shall maintain the study documents and records as specified in "Essential Documents for the Conduct of a Clinical Trial" (ICH E6 Section 8), and as required by the applicable regulatory requirement(s). This includes, but is not limited to the protocol, Case Report Forms (CRF)s, AE reports, subject source data (original records or certified copies), correspondence with health authorities and IRB/IEC, consent forms, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject source data must be maintained as original records or copies certified after verification as being accurate and complete. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents.

14.7 STUDY MONITORING

The Sponsor or designee will monitor this clinical study through study site visits scheduled to check the adequacy of site staff and facilities and to ensure adherence to the protocol, study procedures, and applicable regulations. The site monitor will also assess proper CRF completion and source document retention. The Investigator and study site staff are expected to provide adequate space for monitoring visits and to allocate sufficient time to permit adequate review of the study's progress. The Investigator will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents including electronic medical records and study related facilities (e.g., pharmacy, diagnostic laboratories).

14.8 ELECTRONIC DATA RECORD AND CASE REPORT FORMS

Where referenced in this protocol, CRFs refer to electronic CRFs, as defined for the study. A CRF must be completed for each subject who has given informed consent. In the case of screening failure, the following data will be entered into the CRF at a minimum: visit date, demography and reason for screen failure. All entries into the CRF are ultimately the responsibility of the Investigator before adding his/her signature.

The CRF must be completed at the time of, or shortly after the subject's visit, with the exception of results of tests performed outside the Investigator's office, so that they always reflect the latest observations of the subjects participating in the study. If certain information is Not Done, Not Available or Not Applicable, the Investigator must record this according to the CRF completion instructions.

The CRF and source documents must be made available to the site monitor. During monitoring visits, the site monitor will review the CRF entries and evaluate them for completeness and consistency. The CRF entries will also be compared with the source documents to ensure that there are no discrepancies for critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. The site monitor may query the data,

but cannot edit CRF entries recorded by the site designee. A copy of each subject's CRF will be maintained by the Investigator.

14.9 DRUG ACCOUNTABILITY

The investigational drug is to be prescribed only by the Principal Investigator or physician sub-Investigators named on the Form FDA 1572 or foreign equivalent. Under no circumstances will the Investigator(s) allow the investigational drug to be used other than as directed by this protocol.

The Investigator must maintain accurate records accounting for the receipt of the investigational drug supplies and for the disposition of the drug. Documentation of the disposition of the drug should consist of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing, and any unused drug returned. This record is in addition to any drug accountability information recorded on the case report forms. At the termination of the study or at the request of the Sponsor, the Investigator must return any unused study medications and all partially dispensed or empty containers to the Sponsor or its designee according to applicable local and country regulations. If return of drugs is not feasible, the Sponsor will supply instructions as to how the supplies may be destroyed. Drug supply destruction must be clearly documented. Any investigational drug return will be documented at the Sponsor. The Investigator will also provide a written explanation for any missing study drugs.

14.10 RECORD RETENTION

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by the Sponsor's Quality Assurance auditors and by US and non-US regulatory authorities. The period of time these documents must be maintained is governed by US and non-US regulations. International requirements specify that these documents are to be maintained for 15 years or longer after a drug is approved for marketing. The Sponsor or its designee(s) will inform the Investigator when these documents may be destroyed. The Sponsor or its designee(s) must be notified in writing *at least 6 months* prior to the intended date of disposal of any study record related to this protocol to allow the Sponsor to make alternate storage arrangements.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

14.11 FINANCIAL DISCLOSURE

The Investigator's disclosable financial interests must be obtained prior to initiation of the study site, at completion of the study at the investigational site, and 1 year following study completion.

It is the investigator's responsibility to promptly update this information if any relevant changes occur during the above described period. Any disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff to the form FDA 1572 must complete the Investigator Financial Disclosure Form at the beginning of his/her participation in the study.

14.12 INVESTIGATOR'S FINAL REPORT

Each Investigator will submit, shortly after completion of study participation, a final, written report to the Sponsor.

14.13 PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it sponsors. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Sponsor studies should fairly recognize the activities of those that have made a significant contribution to the study [48]. Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators, and others involved such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for clinical studies that are appropriate for this study. Key issues include:

- **Responsibility:** Each Principal Investigator is responsible for the accuracy and completeness of all data from his/her site. The Sponsor (or its representatives) is (are) responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
- **Authorship and Publication Committee:** The Sponsor, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon by all authors before submission for publication.
- **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted to the Sponsor for review and approval and to ensure consistency with the policy in this protocol. The Sponsor will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication. Any Investigator who plans to submit material for publication must adhere to the following procedure for Sponsor review and approval:
  a. The Investigator will notify the Sponsor of his/her intent to publish and/or present results of the study at least 30 days prior to submission for publication or the scheduled presentation date. The notification should be made in writing to the Vice President, Clinical Development.
  b. The Investigator shall provide to the Sponsor the full details of the proposed publication or presentation in electronic format at minimum 14 (fourteen) days prior to submission for publication of any paper, letter or similar publication, or 7 (seven) days prior to submission for presentation of any abstract, poster, talk, or any other presentation.
  c. The Investigator shall give reasonable consideration to any request by the Sponsor to make changes within the periods mentioned in (b) above.

d. The Investigator shall remove confidential information requested by the Sponsor before finalizing the publication.

e. Upon written request from the Sponsor, the Investigator agrees not to submit data for publication/presentation for an additional 60 (sixty) days in order to allow for actions to be taken which might be necessary to preserve rights for patent protection. If such written request is not made within the periods mentioned in (b) above, the Sponsor will be deemed to have waived the right to delay.

f. In any case, the Investigator will also provide a final version, in exactly the form that was submitted for publication, to the Sponsor simultaneously with that submission; this shall also apply to any revised versions that are submitted following review by the journal (etc.) in which publication is projected.

- **Confidentiality:** Investigators will conduct all interactions with the Sponsor and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
- **Medical Journal Review:** Consistent with the intention of the Sponsor to publish the study in a fair and accurate manner, the Sponsor supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, e.g., protocol and amendments, data tabulations, etc. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and the Sponsor will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
- **Internet Clinical Study Listing:** In addition, also consistent with the recommendations of the ICMJE, the Sponsor will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical studies.

14.14 CONFIDENTIALITY

The Sponsor, its designees, and all clinical site personnel affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified *only* by an identification number.

All information concerning this study and the Sponsor's development of emricasan that is not previously published is considered confidential information. This confidential information shall remain the sole property of the Sponsor. It shall not be disclosed to others without written consent of the Sponsor and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by the Sponsor as they deem necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current federal and international regulations, the Investigator is obliged to furnish the Sponsor with complete test results and all data compiled in this study.

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Appendix I. Schedule of Events

		Double-blind Treatment Phase										Follow-up
		Initial 24 weeks							Continued 24 weeks			
	Screening Wk -6 to Day 0	Day 1	Wk 4 ±5 Days	Wk 8 ±7 Days	Wk 12 ±7 Days	Wk 16 ±7 Days	Wk 20 ±7 Days	Wk 24 ±7 Days	Wk 32 ±10 Days	Wk 40 ±10 Days	Wk 48 ±10 Days	2 wks after Wk 24 or 48 ±7 Days
Study Procedures												
Informed consent	X							X				
Eligibility criteria	X	X										
Medical and surgical history	X											
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, weight, Child-Pugh	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[A]	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X		X					X			X	X
AUDIT, Skinner questionnaires	X											
AUDIT-C questionnaire					X			X			X	
Liver/gallbladder ultrasound[B]	X											
Esophagogastroduodenoscopy[C]	X											
SF-36 and CLDQ		X						X			X	
HVPG (with blood samples)	X							X				
Adverse event assessment[D]	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation		X	X	X	X	X	X	X[E]	X	X		
Compliance assessment			X	X	X	X	X	X	X	X	X	
Methacetin breath test[F]	X							X			X	
Transient elastography[F]	X							X			X	

		Double-blind Treatment Phase										Follow-up
		Initial 24 weeks							Continued 24 weeks			
	Screening Wk -6 to Day 0	Day 1	Wk 4 ±5 Days	Wk 8 ±7 Days	Wk 12 ±7 Days	Wk 16 ±7 Days	Wk 20 ±7 Days	Wk 24 ±7 Days	Wk 32 ±10 Days	Wk 40 ±10 Days	Wk 48 ±10 Days	2 wks after Wk 24 or 48 ±7 Days
Laboratory Evaluations												
Chemistry	X[G]	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X[H]	X[H]	X	X	X	X	X	X	X	X	X	X
α-fetoprotein, etiologic screen	X											
Metabolic[I]		X						X			X	
Fibrosis markers		X						X			X	
Transporter genotyping		X										
Population PK			X	X	X	X	X	X	X	X	X	
Biomarkers (peripheral blood)	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[J]	X	X										
Urine pregnancy test[J]		X	X	X	X	X	X	X	X	X	X	X

A Comprehensive physical examination at Screening, Week 24, Week 48. Focused physical examination at all other visits. Height at Screening only.
B If subject had a liver and gallbladder ultrasound within three months of Screening and a report with the required information is available, the prior ultrasound can be used for the study.
C If subject had a prior esophagogastroduodenoscopy (EGD) according to Baveno VI recommendations and a report with the required information is available, the prior EGD can be used for the study.
D Includes assessment for biliary colic symptoms and qualifying clinical outcome events.
E For subjects who sign consent for the second 24-week treatment phase only.
F At select sites.
G AST, ALT, and total and direct bilirubin measured twice during screening at least 2 weeks apart.
H Including quantitative protein and creatinine
I After fasting at least 10 hours.
J For females of reproductive potential.

Appendix II. Measurement of Liver Metabolic Function with the Methacetin Breath Test

The ^{13}C-methacetin breath test (MBT) is a noninvasive tool to assess liver microsomal capacity to metabolize the nonradioactive ^{13}C-labeled Methacetin. The Breath Test System consists of the BreathID® MCS device and a test kit containing a breath collection nasal cannula and a nonradioactive isotope ^{13}C-methacetin solution. The BreathID MCS device measures and computes the $^{13}CO_2/^{12}CO_2$ ratio in the subject's exhaled breath in real time.

Subject will be asked to sit in a chair and the nasal cannula (a small tube) will be placed beside their nostrils. Attached to the nasal cannula will be the BreathID MCS device. The BreathID MCS device will be activated for approximately 10 minutes and it will collect the subject's carbon dioxide while breathing normally. This process can take up to a maximum of 25 minutes if the device needs to self-calibrate.

One cup of a solution of a 75mg Methacetin pre-dissolved in water will be administered to the subject. Methacetin is exclusively broken up in the liver and turns into carbon dioxide and acetaminophen (Tylenol®). The amount of carbon dioxide is measured by the BreathID MCS device, and will indicate the liver's metabolic capacity to metabolize ^{13}C-Methacetin.

Subjects will be asked to remain sitting in a chair with the nasal cannula in their nose breathing in a normal fashion for the next 60 minutes. Then the nasal cannula will be removed and subjects may leave the testing room.

The full breath test procedure could take up to 1.5 hours.

The actual MBT measure that will be used is the $cPDR_{30}$, which is the cumulative percentage dose recovery of the metabolized ^{13}C-methacetin 30 minutes after ingestion of the test substrate. It is obtained using the following steps:

1. All delta over baseline (DOB) measures with corresponding time-point (T_n) will be noted on the CRF. Each DOB will be plotted by the BreathID MCS device using the following formula:
   $DOB = {}^{13}CO_2/{}^{12}CO_2 @T_n - {}^{13}CO_2/{}^{12}CO_2 @T_0$

   Where T_0 is the baseline sample time (0) and T_n is the time of the post ingestion sample in minutes.

2. The DOBs will be transformed into percentage dose recovery rates (PDR) at a specific time point (n) by using the following formula:
   $PDR_n = 0.01817853 \times DOB_n \times w^{0.5378} \times h^{0.3963}$

   While: w = weight (in kg), h = height (in cm)

3. The following formula will be used to obtain $cPDR_{30}$:

$$cPDR_{30} = \frac{\frac{T_1}{60} \cdot PDR_1}{2} + \sum_{i=2}^{n} \frac{\frac{T_n - T_{n-1}}{60} \cdot (PDR_n - PDR_{n-1})}{2} + \frac{T_n - T_{n-1}}{60} \cdot PDR_{n-1}$$

The company developing the breath test, Exalenz Bioscience, will obtain access to the subject's study data including all the breath test parameters as well as the subject's demographic, imaging, and laboratory data. Exalenz Bioscience will be using these data in order to develop and validate diagnostic and/or prognostic, and/or monitoring algorithms for this study population. Exalenz Bioscience may segregate a portion of the subject data for use of approval of the breath test and its algorithm(s).

The following precautions should be observed prior to the MBT:

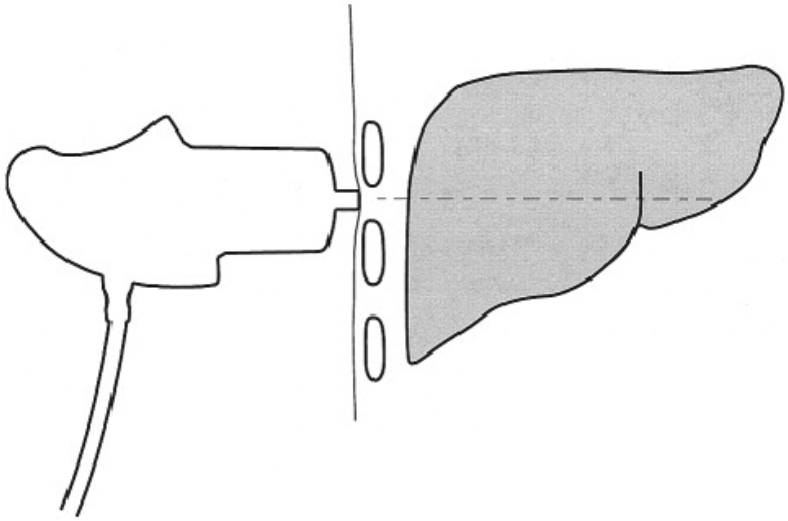
- Subject should be fasting, including all oral morning medications (except for beta blockers and study drug [emricasan or placebo]), for at least 8 hours prior to the MBT
- Subject should not smoke on the day of the breath test prior to the MBT
- Subject should not take any of the following drugs within 48 hours prior to the MBT: acyclovir, allopurinol, carbamazepine, cimetidine, ciprofloxacin, daidzein (herbal), disulfiram, echinacea, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, montelukast, norfloxacin, phenylpropanolamine, phenytoin, propafenone, rifampin, terbinafine, ticlopidine, thiabendazole, verapamil, zileuton or any medication that might interfere with methacetin metabolism or might affect CYP1A2 (cytochrome P450 1A2)
- Subject should not take amiodarone within 30 days prior to the MBT
- Subject should not take paracetamol (acetaminophen) related medications within the 24 hours prior to the MBT
- Subjects should not perform the MBT if allergic or hypersensitive to methacetin or its metabolites (paracetamol, acetaminophen)
- Subject should not consume any alcohol or caffeine within 24 hours prior to the MBT
- Subject should not have general anesthesia or sedation within 24 hours prior to the MBT
- Subjects on beta-blockers or statins should be on stable dose at least 30 days prior to the MBT

Appendix III. FibroScan® Protocol

Background

Transient elastography performed with FibroScan® uses a low frequency vibrator (50Hz) mounted on 1-D US probe (5MHz). The speed of propagation of the shear wave through the liver is proportional to stiffness. The stiffness correlates with the severity of fibrosis.

Figure 5. FibroScan® Probe Placement in Relation to Anatomy of a Subject



Source: Reproduced from Ziol et al 2005

There are three images displayed on the monitor:

1. A-mode image
2. Time movement image
3. 2D elastogram

These images are used by the operator to make sure that the area of the liver selected is free of large vascular structures, that lung fields do not encroach on inspiration and that the selected area is not over a rib. The elastogram demonstrates the depth of the shear wave with time. The slope of the resulting line gives speed of propagation.

Method

1. The subject is asked to lie comfortably in the supine position with his/her right arm fully abducted and resting on a pillow.
2. Cover the tip of the probe with a small amount of coupling gel and place on the skin, on the right lateral wall of the abdomen between the ribs at the level of the right lobe of the liver.
3. The right lobe of the liver is selected to ensure that the area of the liver to be measured is at least 6 cm thick.
4. The probe must be placed perpendicular to the subject's abdominal wall.

5. Pressure should be applied by the operator on the subject and the button is pressed to initiate an acquisition.
   a. It is important to apply enough pressure on the subject so that the pressure bar display is within the green range. Insufficient pressure will be displayed as orange and over pressure will be displayed as red.
   b. Pressure must be released immediately following an acquisition.
   c. When making a measurement, it is also important to ensure that the subject is breathing slowly and not moving or speaking.
6. If a successful reading is not acquired, the probe should be moved up or down by one rib space and, if that is not successful, anteriorly or posteriorly from the initial site by 1cm. Once a successful reading has been obtained, the remaining readings should be taken from the same site.
7. For each subject, the following parameters should be recorded:
   a. The median liver stiffness value kPa
   b. The inter-quartile (IQR) range kPa
   c. Success rate (%)
8. To obtain a reliable and representative evaluation of the stiffness of the liver, the following criteria should be met:
   a. 10 valid measurements should be acquired
   b. Success rate >60%
   c. IQR/median <30%

If any of these criteria are not met, the test should be repeated.

Additional Recommendations

The following recommendations are being provided in order to improve standardization of the FibroScan® procedure. Please implement these recommendations to obtain consistent and reproducible measurements.

1. The subject should be NPO for 4 hours prior to the procedure
2. The operator should be seated next to the subject, with the hand holding the probe, stabilized by the other. This will improve the stability of the probe as it is held up against the patient yielding an improved result with a low IQR.
3. The measurement should be taken during expiration.
4. Investigators should use the appropriate probe (normal or XL) for a subject according to their level of adiposity and use the same probe consistently for all measurements for that subject during the course of the study.

Appendix IV. Diabetes Mellitus Definition and Metabolic Syndrome Criteria

The diagnosis of **diabetes mellitus** is based on criteria established by the American Diabetes Association:

- HbA1c ≥6.5% (using a certified method standardized to the Diabetes Control and Complications Trial assay) OR
- Fasting plasma glucose ≥126 mg/dL (7 mmol/L) (confirmed by repeat testing unless there is unequivocal hyperglycemia) OR
- 2-hr plasma glucose (≥200 mg/dL [11.1 mmol/L) after 75-gram oral glucose tolerance test OR
- Random plasma glucose ≥200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia or hyperglycemic crisis

The metabolic syndrome is a cluster of risk factor for cardiovascular disease and type 2 diabetes mellitus including elevated blood pressure, dyslipidemia (elevated triglycerides and low HDL cholesterol), elevated fasting glucose, and central obesity. Various diagnostic criteria have been proposed by different scientific organizations in the past, with the main difference concerning the measure for central obesity. In 2009, the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity issued a joint statement proposing a harmonized definition of the metabolic syndrome [49]. The criteria for diagnosis are summarized in Table 1 and Table 2.

Table 1. Criteria for Clinical Diagnosis of the Metabolic Syndrome

Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

HDL-C indicates high-density lipoprotein cholesterol.

*It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.

†The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose ω-3 fatty acids presumes high triglycerides.

‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

Source: Alberti et al. Circulation, 2009. **120**(16): p. 1640-5.

Table 2. Current Recommended Waist Circumference Thresholds for Abdominal Obesity by Organization

		Recommended Waist Circumference Threshold for Abdominal Obesity	
Population	Organization (Reference)	Men	Women
Europid	IDF (4)	≥94 cm	≥80 cm
Caucasian	WHO (7)	≥94 cm (increased risk) ≥102 cm (still higher risk)	≥80 cm (increased risk) ≥88 cm (still higher risk)
United States	AHA/NHLBI (ATP III)* (5)	≥102 cm	≥88 cm
Canada	Health Canada (8,9)	≥102 cm	≥88 cm
European	European Cardiovascular Societies (10)	≥102 cm	≥88 cm
Asian (including Japanese)	IDF (4)	≥90 cm	≥80 cm
Asian	WHO (11)	≥90 cm	≥80 cm
Japanese	Japanese Obesity Society (12)	≥85 cm	≥90 cm
China	Cooperative Task Force (13)	≥85 cm	≥80 cm
Middle East, Mediterranean	IDF (4)	≥94 cm	≥80 cm
Sub-Saharan African	IDF (4)	≥94 cm	≥80 cm
Ethnic Central and South American	IDF (4)	≥90 cm	≥80 cm

*Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for CVD and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.

Source: Alberti et al. Circulation, 2009. **120**(16): p. 1640-5.

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