GT-031 (NAVIGATE) Protocol

Study Title: A Seamless, Adaptive, Phase 2b/3, Double-Blind, Randomized, Placebo-controlled, Multicenter, International Study Evaluating the Efficacy and Safety of Belapectin (GR-MD-02) for the Prevention of Esophageal Varices in NASH Cirrhosis

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Protocol

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Investigational Product: Belapectin (GR-MD-02)

Protocol Reference Number: GT-031 (NAVIGATE)

[redacted]

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INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein.

Printed name and qualifications: _____

Signature: _____

Date: _____

Name and address of site: _____

_____

_____

_____

SYNOPSIS

Title of study: A Seamless, Adaptive, Phase 2b/3, Double-Blind, Randomized, Placebo-controlled, Multicenter, International Study Evaluating the Efficacy and Safety of Belapectin (GR-MD-02) for the Prevention of Esophageal Varices in NASH Cirrhosis

Indication: Primary prevention of esophageal varices in patients with clinical signs of portal hypertension and compensated non-alcoholic steatohepatitis (NASH) cirrhosis

Number of Investigators and study centers: Multinational; in approximately 150 sites

Development phase: Phase 2b/3

Objectives and endpoints:

In this seamless, adaptive, two-stage Phase 2b/3 trial in patients with NASH cirrhosis and clinical signs of portal hypertension but without esophageal varices at baseline, an interim analysis (IA) will occur during Stage 1 of this trial (Phase 2b, after 78 weeks [18 months] of treatment), and then following any adaptive modifications based on that IA, the trial will continue seamlessly into Stage 2 (Phase 3, with 78 weeks [18 months] of treatment).

The objectives and endpoints for Phase 2b and Phase 3 are stated below. Endpoints are applied independently to 2 groups of patients: patients who enter at the beginning of Phase 2b (Stage 1) and continue through to the end of Phase 3 (Stage 2) (for a total of 156 weeks [36 months] participation), and new patients randomized only into Phase 3 (for a total of 78 weeks [18 months] participation).

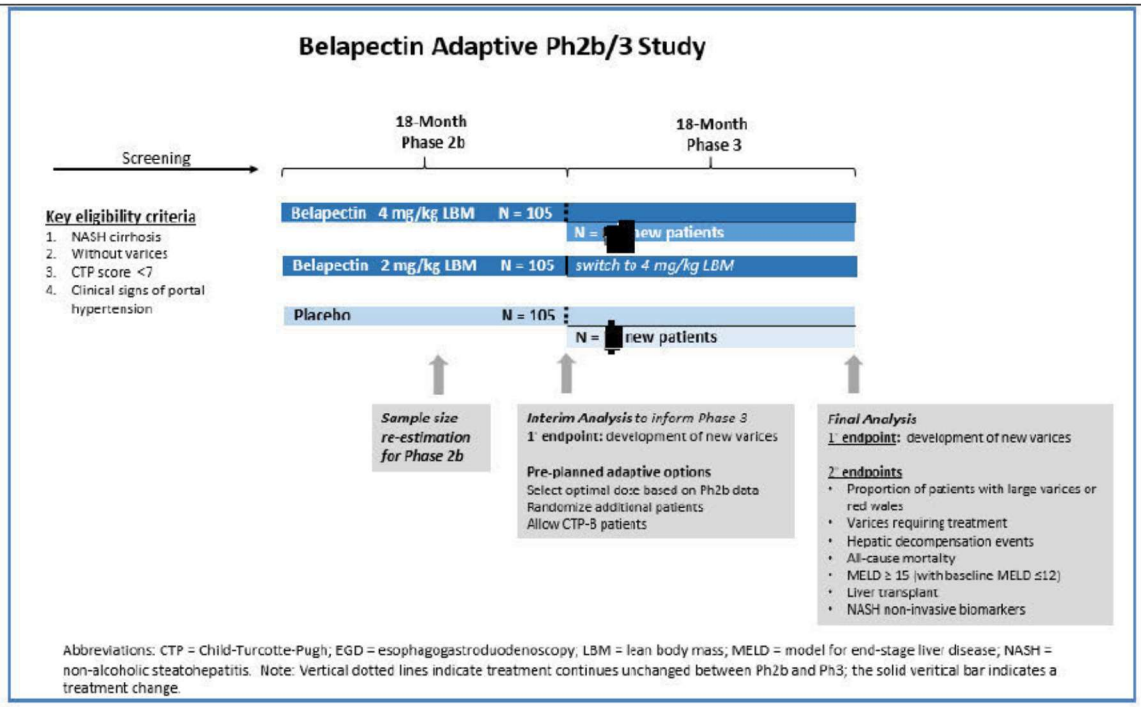
Objectives	Endpoints
Primary Efficacy Objective	**Primary Efficacy Endpoint**
To evaluate the efficacy of 2 mg/kg and 4 mg/kg lean body mass (LBM) of belapectin (GR-MD-02) compared to placebo in preventing the development of esophageal varices	Proportion of patients in the belapectin treatment groups who develop esophageal varices at 78 weeks (18 months) of treatment compared to placebo
Key Secondary Efficacy Objective	**Key Secondary Efficacy Endpoint**
To evaluate the effect of belapectin on composite clinical outcomes	Incidence rate of patients in the belapectin treatment groups, compared to placebo, who develop any of the following: 1) varices (esophageal or gastric) requiring treatment, 2) variceal bleed requiring hospitalization, 3) clinically significant ascites requiring hospitalization, 4) spontaneous bacterial peritonitis, 5) overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization), 6) mortality (all-cause), 7) liver transplant, 8) model for end-stage liver disease (MELD) score ≥15 on 2 consecutive occasions
Additional Secondary Efficacy Objectives	**Additional Secondary Efficacy Endpoints**
To evaluate the effect of belapectin on progression of esophageal varices	Incidence rate of patients in the belapectin Phase 3 treatment group who progress to large esophageal varices or develop red wales compared to placebo
To evaluate the effect of belapectin treatment on liver cirrhosis-related clinical events	Event-free survival by time to first cirrhosis-related clinical event, including the following: • progression to large varices or red wales • esophageal variceal hemorrhage requiring hospitalization

	• clinically significant ascites requiring hospitalization • spontaneous bacterial peritonitis • overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization) • Child-Turcotte-Pugh (CTP) score increase of ≥2 points (from baseline) on 2 consecutive occasions • MELD score increase to ≥15 as measured on 2 consecutive occasions • liver transplant • liver-related death
Exploratory Efficacy Objectives	**Exploratory Efficacy Endpoints**
To evaluate the effect of belapectin compared to placebo on liver fibrosis	Change in liver stiffness measurement, baseline-adjusted, as determined by vibration-controlled transient elastography (VCTE) (FibroScan) exams during Phase 2b and Phase 3
To evaluate the effect of belapectin compared to placebo on portal hypertensive gastropathy (PHG)	• Difference in development of PHG between belapectin treated and placebo patients • Difference in resolution or improvement in PHG between belapectin treated and placebo patients
To assess the effect of belapectin compared to placebo on health-related quality of life	Difference in Chronic Liver Disease Questionnaire scores between belapectin and placebo treatment during Phase 2b and Phase 3
Safety Objectives	**Safety Endpoints**
To assess the safety and tolerability of belapectin compared to placebo treatment	The safety endpoints include: • incidence and nature of adverse events (AEs), including adjudicated drug-induced liver-injury (DILI) and adjudicated cardiovascular events (Major Adverse Cardiac Event [MACE]) • changes from baseline in physical examinations, vital signs, and electrocardiogram (ECG) parameters • changes from baseline in routine central laboratory tests (clinical chemistry, hematology), including liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transferase [GGT], alkaline phosphatase [ALP)], and liver function markers (bilirubin, albumin, international normalized ratio [INR])
PK Objective	**PK Endpoint**
To produce a population PK model of belapectin	Plasma belapectin concentrations and PK parameters (area under the curve, maximum observed plasma concentration, time of the maximum observed plasma concentration, apparent terminal elimination half life) in Phase 2b (a minimum of 30 patients per treatment group) and in Phase 3 (a minimum of 30 patients per treatment group)

Methodology/study design:

This is a seamless, adaptive, two-stage Phase 2b/3, randomized, double-blind, multicenter, parallel-groups, placebo-controlled study of patients with NASH cirrhosis and clinical signs of portal hypertension but without esophageal varices at baseline. See Figure 1 (below) and Figure 2 (Section 3.1 of the protocol).
The first stage of this study, Phase 2b, will randomize approximately 315 patients in a 1:1:1 ratio (105 patients per group) to belapectin 2 mg/kg LBM or 4 mg/kg LBM or placebo, administered intravenously (IV) every other week for 78 weeks (18 months). During Phase 2b, a non-comparative (blinded) sample size re-estimation (SSR) procedure will be conducted when at least 50% of patients complete 78 weeks (18 months) of Phase 2b treatment, to confirm initial sample size assumptions. Additional patients may then be enrolled in Phase 2b, up to a maximum of 65 additional patients in each Phase 2b treatment group, without requiring a protocol amendment. When all enrolled patients in Phase 2b (Stage 1) have completed 78 weeks (18 months) of treatment, an IA will occur to select the optimal belapectin dose and to confirm the patient sample size for the second stage, Phase 3. The IA could also lead to study termination for futility (per decision criteria defined in the Statistical Analysis Plan [SAP]). An independent Data Safety Monitoring Board (DSMB) will oversee the IA and make recommendations on adaptive modifications to an independent Trial Steering Committee (TSC). The IA and potential study adaptations, including SSR procedures, are summarized in this protocol and outlined in detail in the SAP. The DSMB will follow procedures detailed in the separate DSMB Charter, to ensure study integrity.

Patients who complete Phase 2b will continue into Phase 3 for 78 additional weeks(18 additional months), to continue treatment with belapectin (at the same or a modified dose*) or to continue treatment with placebo. For patients who start Phase 3 prior to the IA, they will similarly continue on their current treatment until IA and may be switched to a modified dose based on the results of the IA. Patients who switch to the optimal belapectin dose will be analyzed separately. [*For example, if the 4-mg/kg LBM dose was chosen at the IA as the optimal dose for Phase 3, then the patients who received the 2-mg/kg LBM dose in Phase 2b will be switched to the 4-mg/kg LBM dose for the remainder of their Phase 3 participation.] Phase 3 has a parallel-groups design comparing the optimal dose level of belapectin to placebo. Approximately [redacted] additional patients will be enrolled directly into Phase 3, in a 2:1 ratio to the optimal belapectin dose (approximately [redacted] patients) or placebo (approximately [redacted] patients), respectively. However, contingent on IA results, a total of up to [redacted] additional patients could be enrolled directly in Phase 3, without requiring a protocol amendment.



Stage 1: Phase 2b

Identification of Patients: Prior to signing the informed consent, potential patients will be identified per local standard of care for a diagnosis of NASH cirrhosis (including a historic liver biopsy, if available), and presence or absence of esophageal varices (based on historic esophagogastroduodenoscopy [EGD], if available).

Screening: Following the signing of the informed consent, assessments for eligibility (by inclusion and exclusion criteria) will occur within 10 weeks (2.5 months) before randomization, as follows:

- Medical, surgical and medication history, vital signs (heart and respiratory rate, blood pressure [BP], and body temperature), complete physical examination, including height and weight, ECG, and central clinical laboratory evaluations (hematology, chemistry, coagulation profile, urinalysis, specialized tests for specific liver diseases, and pregnancy test [for women of childbearing potential]).
- Clinical signs of portal hypertension, with either one of the following: (a) platelet count <150,000/mm^3 (from central laboratory or historical record, such as detailed chart notes providing platelet numbers or copies of laboratory reports showing platelet count[s] below 150,000/mm^3) or (b) documented HVPG measurement >6 mmHg
  OR
  (c) at least two of the following: spleen size ≥14 cm by imaging (ultrasound, magnetic resonance imaging [MRI], or computed tomography [CT] scan), evidence of abdominal collateral circulation (by ultrasound, MRI, or CT scan or caput medusae seen upon physical examination), or documented liver transient elastography (eg, FibroScan) ≥20 kPa or AST/ALT >1.
- EGD with video recording documentation to confirm the presence or absence of esophageal varices.
- Liver and abdomen ultrasound exam, to screen for hepatocellular carcinoma (HCC) and for ascites.
- Liver biopsy, while not required, can be used to confirm diagnosis of NASH cirrhosis by the central study pathologist, if necessary. (A historic liver biopsy is acceptable but the biopsy

blocks and/or slides must be available for central review, if this is the main/only confirmation being used for evidence of NASH cirrhosis.) Results from the central study pathologist must be available before the patient is randomized.

Note: It is not required for all of the assessments above to be performed on the same day.

Randomization/Treatment: Patients meeting all inclusion and no exclusion criteria will be randomized (1:1:1) to 1 of 3 treatments: placebo, belapectin 2 mg/kg or 4 mg/kg LBM, administered IV every other week for 78 weeks (18 months). Randomized patients will be stratified by type 2 diabetes status.

Patients who complete Phase 2b (Stage 1) will continue into Phase 3 (Stage 2). Those patients who received belapectin during Phase 2b will continue belapectin treatment during Phase 3 at the dose chosen at the IA. Those patients who received placebo during Phase 2b will continue placebo treatment during Phase 3.

The following efficacy assessments will be performed:

- EGD with video recording documentation, to assess varices at the end of Phase 2b (Week 78) or upon early discontinuation at any visit. An independent endoscopy review expert panel will review all EGD records (including the baseline EGD), and adjudicate all assessments.
- Transient elastography (eg, FibroScan) to assess liver stiffness, at approximately 6 month intervals.
- Blood samples for liver enzymes (eg, ALT, AST, ALP, GGT) and liver function markers (eg, bilirubin, albumin, INR) and platelet counts will also be drawn periodically, together with routine central clinical laboratory tests for safety monitoring during planned study center visits, as indicated in the protocol Schedule of Assessments.
- At the start and end of Phase 2b, blood samples will be stored (-80°C) for other possible post-study biomarker tests and gene expression analysis.

Early Termination and Final Visits: Patients who discontinue Phase 2b early (prior to Week 78) will have an Early Termination Visit (14 to 28 days after their last dose), a final visit (End of Study Visit [EOS]) 14 days after the Early Termination Visit, and will not be eligible to participate in Phase 3.

Interim Analysis:

A pre-specified IA of efficacy and safety data will be conducted after all planned patients in Phase 2b (Stage 1) have completed 78 weeks (18 months) of treatment. The purpose of the IA is to allow potential adaptive modifications of the study, including: (1) select the optimal dose of belapectin for Phase 3 (Stage 2), (2) re-estimate the patient sample size for Phase 3, (3) re-evaluate the treatment allocation ratio for Phase 3, (4) re-evaluate the inclusion and exclusion criteria for Phase 3, including the CTP status, (5) and/or terminate the study.

An Interim Analysis Charter will specify the membership and roles of an independent DSMB and TSC, the IAs adaptive rules and decision criteria that define potential modifications of the study, and the operational procedures to preserve study blinding and integrity.

Stage 2: Phase 3

Identification of new patients entering Phase 3: Prior to signing the informed consent, potential patients will be identified per local standard of care for a diagnosis of NASH cirrhosis (based on historic liver biopsy, if available), and presence or absence of esophageal varices (based on historic EGD, if available).

Screening: Following the signing of the informed consent, assessments for eligibility (by inclusion and exclusion criteria) will occur within 10 weeks (2.5 months) before randomization, as follows:

- Medical, surgical and medication history, vital signs (heart and respiratory rate, BP, and body temperature), complete physical examination, including height and weight, ECG, and central clinical laboratory evaluations (hematology, chemistry, coagulation profile, urinalysis,

specialized testing for specific liver diseases, and pregnancy test [for women of childbearing potential]).

- Clinical signs of portal hypertension, with either one of the following: (a) platelet count <150,000/mm^3 (from central laboratory or historical record, such as detailed chart notes providing platelet numbers or copies of laboratory reports showing platelet count[s] below 150,000/mm^3) or (b) documented HVPG measurement >6 mmHg
  OR
  (c) at least two of the following: spleen size ≥14 cm by imaging (by ultrasound, MRI, or CT scan), evidence of abdominal collateral circulation (by ultrasound, MRI, or CT scan or caput medusae seen upon physical examination), or documented liver transient elastography (eg, FibroScan) ≥20 kPa or AST/ALT >1.
- EGD with video recording documentation to assess the absence/presence of esophageal varices.
- Liver and abdomen ultrasound exam, to screen for HCC and for ascites.
- Liver biopsy, while not required, can be used to confirm diagnosis of NASH cirrhosis by the central study pathologist, if necessary. (A historic liver biopsy is acceptable but the biopsy blocks and/or slides must be available for central review, if this is the main/only confirmation being used for evidence of NASH cirrhosis.) Results from the central study pathologist must be available before the patient is randomized.

Note: It is not required for all of the assessments above to be performed on the same day.

Treatment: Patients meeting all inclusion and no exclusion criteria will be randomized in a 2:1 ratio to either belapectin X mg/kg LBM IV (the optimal dose, either 2 mg/kg or 4 mg/kg LBM), or placebo, dosed every other week for 78 weeks (18 months).
The following efficacy assessments will be performed:

- EGD with video documentation, to assess varices at the end of Phase 3 or upon early discontinuation at any visit. An independent endoscopy review expert panel will review all EGD records (including the baseline EGD), and adjudicate all assessments.
- Transient elastography (eg, FibroScan) to assess liver stiffness, approximately every 6 months
- Blood samples for liver enzymes (eg, ALT, AST, ALP, GGT) and liver function tests (eg, bilirubin, albumin, INR) and platelet counts will also be drawn periodically, together with routine central clinical laboratory tests for safety monitoring during scheduled study center visits, as indicated in the protocol Schedule of Assessments.
- At the start (for newly-enrolled patients) and end of Phase 3, and at time points indicated in the schedule of assessments, a blood sample will be stored (-80°C) for other possible post-study biomarker tests and gene expression analysis.

Final Visit and Early Termination/ End of Treatment Visit: All patients, discontinuing early and completing Phase 3, will have an Early Termination Visit or End of Treatment Visit 14 to 28 days after their last dose. They will then have a final visit (EOS Visit) 14 days after the Early Termination Visit or End of Treatment Visit.

Number of patients:
Phase 2b (Stage 1): Approximately 315 patients will be randomized into 3 parallel treatment groups in a 1:1:1 ratio, with approximately 105 patients in each of the 3 treatment groups.
A blinded SSR (based on a non-comparative assessment of the incidence rate of new varices) will occur during Phase 2b (when at least [redacted]% of Phase 2b patients have completed 78 weeks [18 months] of treatment). Based on that re-estimation, up to [redacted] patients ([redacted] additional patients in each treatment arm) potentially could be enrolled in Phase 2b (Stage 1) for a total number of [redacted] patients ([redacted].
Phase 3 (Stage 2): Up to [redacted] patients completing Phase 2b will continue in Phase 3 for the full 156 week (36 month) participation either with the belapectin dose chosen at the IA or with placebo treatment.

In addition, approximately [redacted] new patients are planned for enrollment in Phase 3 after the IA (approximately [redacted] on the optimal belapectin dose and approximately [redacted] on placebo), for a total number of [redacted] patients. Depending on the results of the IA, an additional [redacted] patients might be enrolled without a protocol amendment. This would bring the total of new patients enrolled directly into Phase 3 to approximately 5[redacted] patients (approximately [redacted] on the optimal belapectin dose and approximately [redacted] on placebo) and the total number of patients that may be enrolled in this Phase 2b/3 trial without a protocol amendment to approximately [redacted] patients ([redacted]

Sample size rationale:
Assuming [redacted] patients [redacted] patients per group) are enrolled in Stage 1 (Phase 2b), all patients on the optimal belapectin dose and placebo continue into Stage 2 (Phase 3), and an additional [redacted] patients are enrolled and randomized (in a 2:1 ratio with [redacted] to the optimal belapectin dose and [redacted] to placebo, respectively), and also assuming an annual incidence rate of new varices of [redacted]%, and a [redacted]% patient dropout rate, then the study is estimated to provide at least [redacted]% power, with a 1-sided significance level of [redacted], for detecting an annual relative risk reduction of [redacted]% for the primary efficacy endpoint (incidence of new varices) at 78 weeks [18 months] of treatment.

With this planned sample size ([redacted] patients [redacted]] in the belapectin optimal treatment group and [redacted] [redacted]] in the placebo group), this study is estimated to also provide at least [redacted]% power (1-sided significance level of [redacted]) for detecting a 50% relative risk reduction in the key secondary efficacy endpoint (composite incidence of liver-related clinical outcome events, 78 weeks [18 months] cumulative), assuming an annual incidence rate as low as 8%.

The assumed yearly incidence rate of new varices of 1[redacted]% is based on data from a prior belapectin Phase 2 study (GT-026) in a subset of patients without esophageal varices at baseline who subsequently developed varices over 1 year of follow-up (mean rate = [redacted]%; [redacted]% confidence interval [CI]: [redacted]%, [redacted]%). The actual incidence rate of new varices in this Phase 2b/3 study may be different. Therefore, to minimize the possibility of under-powering this trial, two adaptive modifications of the patient sample size are planned:

1) During Stage 1 (Phase 2b) when at least [redacted]% of patients complete 78 weeks (18 months) of treatment, a non-comparative (blinded) SSR procedure will occur. If the observed incidence rate of new varices is less than was initially assumed, up to a maximum of [redacted] additional patients in each treatment arm may be enrolled without requiring a protocol amendment.

2) During the IA (to occur when all patients in Stage 1 [Phase 2b] have completed 78 weeks [18 months] of treatment), the sample size may also be adjusted to attain a conditional power ≥[redacted] for the primary efficacy analysis.

Overall, the total number of patients enrolled in this trial (Phase 2b + Phase 3) may not exceed [redacted] without a protocol amendment.

Diagnosis and main criteria for inclusion and exclusion:
Phase 2b: Patients age ≥18 and ≤75 years, with a diagnosis of NASH cirrhosis, no esophageal varices on EGD with video recording documentation, CTP score <7, and clinical evidence of portal hypertension with either one of the following: (a) platelet count <150,000/mm^3 (from central laboratory or historical record, such as detailed chart notes providing platelet numbers or copies of laboratory reports showing platelet count[s] below 150,000/mm^3) or (b) documented HVPG measurement >6 mmHg, OR, (c) at least two of the following: spleen diameter ≥14 cm (based on imaging), evidence of abdominal collateral circulation (by imaging or physical examination), or documented liver transient elastography (eg, FibroScan) ≥20 kPa or AST/ALT >1.

For Phase 3, new patients: The inclusion/exclusion criteria for Phase 3 are currently the same as for Phase 2b. Eligibility will be reviewed by the DSMB as part of the IA, and may be modified (with approval of relevant Ethics Committees/Institutional Review Boards) to ensure patient safety.
Test products, dose, and mode of administration: **Phase 2b**: Belapectin 2 mg/kg LBM or 4 mg/kg LBM, diluted in 100 mL of normal saline, infused IV via a peripheral vein over 60 minutes (± 12 minutes). **Phase 3**: Optimal dose level of belapectin (to be selected by the DSMB, and approved by the TSC), based on the IA after Phase 2b. Note: For patients who start Phase 3 prior to the IA, they will continue on their current treatment until IA and may be switched to a modified dose based on the results of the IA. No dose modification for an individual will occur unless body mass index increases ≥10% above baseline.
Reference therapy, dose, dose form, and mode of administration: Placebo to match belapectin, diluted in 100 mL normal saline and infused IV via a peripheral vein over 60 minutes (± 12 minutes).
Duration of patient participation in study: Planned Identification of Patients and Screening: 10 weeks (2.5 months) Planned treatment, Phase 2b: 78 weeks (18 months) Planned treatment, Phase 3: 78 weeks (18 months) Planned follow-up (after last dose of study drug): up to 6 weeks Total duration of participation: approximately 170 weeks (± 2 weeks) (approximately 40 months)
Study populations: The following analysis populations for combined Phase 2b and Phase 3 data will be included: **Full Analysis Set (FAS):** all enrolled patients who have been randomized in either Phase 2b or Phase 3. The main efficacy analysis will be based on the FAS. **Modified Full Analysis Set (mFAS)**: all patients in the FAS who receive at least 1 dose of study drug and have at least 1 EGD assessment (with video recording documentation) of esophageal varices. Supportive analysis of the primary and key secondary endpoints will be based on the mFAS Set. **Per-protocol Set (PPS):** all patients in the FAS who receive at least 1 dose of study drug and do not have any important protocol deviations leading to exclusion from the PPS. The validity of patients to the PPS will be reviewed and determined before database lock. **Safety Set (SAF):** all randomized patients receiving at least 1 dose of study drug. The SAF will be the primary analysis population for safety analyses. **PK Set:** all randomized patients who receive at least one dose of study drug and contribute PK measurements to allow for calculation of PK parameters. A minimum of 90 patients (with a minimum of 30 patients per treatment group) from Phase 2b and a minimum of 60 patients (with a minimum of 30 patients per treatment group) from Phase 3 will have PK assessments. In addition, the following analysis populations will be defined for Phase 2b as supportive analyses: **Phase 2b FAS**: all patients who have been randomized and enrolled in Phase 2b. This set will be used to summarize the efficacy of all belapectin dose groups in Phase 2b. **Phase 2b SAF Set**: all patients who have been randomized and receive at least 1 dose of study drug in Phase 2b. This set will be used to summarize the safety in Phase 2b. The FAS, mFAS, PPS, and Phase 2b FAS will be analyzed according to the randomized treatment. The SAF, PK Set, and Phase 2b SAF will be analyzed according to the treatment they actually receive.

Evaluation: Efficacy

Efficacy measures in both Phase 2b and Phase 3 include: EGD with video recording documentation, VCTE (FibroScan), and cirrhosis complications, including the following:

- new esophageal or gastric varices (by EGD, with video recording)
- progression of varices after baseline (large varices or red wales)
- variceal hemorrhage requiring hospitalization
- clinically significant ascites requiring hospitalization
- spontaneous bacterial peritonitis
- overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization)
- CTP score increase from baseline of ≥2 points as measured on 2 consecutive occasions
- MELD score increase to ≥15 as measured on 2 consecutive occasions
- liver transplant
- liver-related deaths

All cirrhosis-related complications (above), as well as all-cause mortality, including MACE (defined for this study as myocardial infarction, hospitalization for unstable angina, stroke/transient ischemic attack, and heart failure) will be adjudicated by the Clinical Events Committee (CEC).

Evaluation: Pharmacokinetics

Plasma belapectin concentrations will be assayed in a minimum of 90 patients (with a minimum of 30 patients per treatment group) in Phase 2b. When a patient consents to PK collection, one patient will contribute PK blood samplings during the first 5 infusion visits (Visit 1, Visit 2, Visit 3, etc.) with blood sampling times at:

- Infusion Visit 1: pre-infusion (within 1 hour before the first infusion) and 3 hours after completing the first infusion
- Infusion Visit 2: 3 hours after the infusion and 24 to 48 hours after completing the second infusion
- Infusion Visit 3: 3 hours after the infusion and 3 to 4 days after completing the third infusion
- Infusion Visit 4: 3 hours after the infusion and 5 to 6 days after completing the fourth infusion
- Infusion Visit 5: pre-infusion sampling (within 1 hour before the infusion) and 3 hours after completing the fifth infusion.

Similar PK assessments will be repeated in a minimum of 60 patients (a minimum of 30 patients per treatment group) during Phase 3.

Evaluation: Safety

Safety assessments will include incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent changes in physical examinations, vital signs, ECGs, and central clinical laboratory test results, including assessment of DILI and MACE.

All patients receiving at least 1 dose of study drug will be evaluated for safety. The safety analyses will include evaluation of the incidence of TEAEs, Grade 3 or greater AEs, serious AEs (SAEs), and TEAEs leading to discontinuation of study treatment. AEs grading will use the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

A DSMB will periodically monitor the trial for safety and include at least 3 independent experts, two physicians, and a statistician. A DSMB charter will be established. The DSMB will meet at pre-determined intervals during the study and at any other times should study monitors or principal investigators consider a review warranted. If more than 6 patients develop an SAE of NCI-CTCAE Grade 3 or 4 that an Investigator considers related to study drug, then the DSMB will evaluate unblinded trial data and consider recommendations on stopping the trial.

All cirrhosis-related complications, as well as all-cause mortality, including MACE (defined as myocardial infarction, hospitalization for unstable angina, stroke/transient ischemic attack, and heart failure), will be adjudicated by the CEC.

Evaluation: Biomarkers

[redacted]

Statistical Methods:

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed with SAS® software, version 9.4 or higher.

Descriptive statistics for continuous variables in summary tables will include the number of patients in the analysis (n), mean, standard deviation, median, and range (minimum, maximum). Descriptive statistics for categorical variables in summary tables will include counts and percentages. In general, statistical tests will be 2-sided at the significance level of alpha = [redacted] or 1-sided with alpha = [redacted]. Two-sided [redacted]% CIs will be produced. Categorical endpoints will be summarized by the number and percentage with a [redacted]% CI for the percentage. Time-to-event endpoints will be summarized and displayed graphically using the Kaplan-Meier (KM) method to estimate the median, and the 25th and 75th percentiles. Continuous endpoints with more than 1 post-baseline measurement will be analyzed using a Mixed Effects Model for Repeated Measures model.

Patient demographics as well as medical and social history, and other baseline patient characteristics (including prior NASH treatments) will be summarized by treatment group. Randomized patients will be stratified by type 2 diabetes status.

Methods for dealing with missing data including dates, and analyzing efficacy and safety results will be specified in the SAP.

Primary analysis

The primary estimand is the proportion of patients (at 78 weeks [18 months]) who develop new esophageal varices in the FAS. The intercurrent events including treatment discontinuation and use of rescue therapy will be handled using the composite strategy. Estimands will be further defined in the SAP.

The global null hypothesis (H0) and alternative hypothesis (Ha) are:

H0: [redacted]

Ha: [redacted]

where p0 denotes the proportion (at 78 weeks [18 months]) of patients with development of esophageal varices in placebo group, and p1 and p2 denote the proportion in the 2 dose groups of belapectin. Suppose p1 is the proportion of the selected optimal dose group.

The individual null hypothesis and alternative hypothesis are:

H10: [redacted]

H20: [redacted]

The null hypotheses will be tested at a 1-sided significance level of [redacted]. The individual p-value comparing the proportions between active dose groups of belapectin and placebo group will be based on standardized test Z statistics for the difference of the proportions. For final analysis at the end of the study, the p-values obtained from both stages will be combined using the 'Inverse Normal' method to ensure the overall type I error is protected at the nominal level regardless of the type of design modifications (including sample size adjustment) at an IA. The 2-stage combined p-value will be calculated for each hypothesis as described above. In order to reject the H10 to claim the selected optimal dose is superior to placebo at the end of the study, both H10 and H0 must be rejected at the pre-specified 1-sided alpha level of [redacted]. The details of the testing procedures will be specified in the SAP.

The number and percentage (ie, proportion) of patients who develop esophageal varices up to 78 weeks (18 months) during Phase 2b and Phase 3 will be presented by treatment group in the FAS. The 95% exact binomial CIs of the proportions and of the difference between each belapectin group and the placebo group will be estimated.

The supportive estimands include those similar to the primary estimand but defined in the mFAS and in the PPS, and the proportion of patients (annual rate) who develop new esophageal varices in the FAS regardless of intercurrent events.

Secondary analysis

The key secondary efficacy endpoint (composite events, in bullet list below) will be analyzed in the FAS as main analysis, and in the mFAS and PPS as supportive analysis:

- Cumulative incidence rate of patients in the belapectin treatment groups, compared to placebo, who develop any of the following:
  - varices (esophageal or gastric) requiring treatment
  - variceal bleed requiring hospitalization
  - clinically significant ascites requiring hospitalization
  - spontaneous bacterial peritonitis
  - overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization)
  - mortality (all-cause)
  - liver transplant
  - MELD score ≥15 on 2 consecutive occasions.

The cumulative incidence rate at 78 weeks [18 months] for a treatment group will be calculated as (number of patients with the event / total time at risk in weeks over all patients) * 78 weeks. The risk duration is from the first dosing date to the date of the first event. For patients who have no events reported, the risk duration is from the first dosing date to the end of follow-up in the study. The difference of the cumulative incidence rate at 78 weeks [18 months] between 2 groups, the associated [redacted]% CI and p-value will be calculated using the method proposed by Liu et al, 2006.

The other secondary endpoints will be analyzed descriptively in the FAS including:

- Cumulative incidence rate at 78 weeks [18 months] of patients in the belapectin treatment groups who progress to large varices or develop red wales, compared to placebo
- Event-free survival by time to a first cirrhosis-related clinical event, including the following:
  - progression to large varices or red wales
  - esophageal variceal hemorrhage requiring hospitalization
  - clinically significant ascites requiring hospitalization
  - spontaneous bacterial peritonitis
  - overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization)
  - CTP score increase of ≥2 points (from baseline) on 2 consecutive occasions
  - MELD score to ≥15 as measured on 2 consecutive occasions
  - liver transplant
  - liver-related death.

Event-free survival will be analyzed using the KM method as described above.

Exploratory analysis

The analyses of the exploratory endpoints will be performed descriptively in the FAS. The categorical endpoints will be summarized by the number and percentage with a 95% CI for the percentage. Continuous endpoints with more than 1 post-baseline measurement will be analyzed using a Mixed Effects Model for Repeated Measures model.

Safety analysis

Safety analyses will be presented for the SAF and the Phase 2b SAF Set.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by MedDRA system organ class and preferred term. Events from the time of the patient signing informed consent/assent must be reported. Adverse events prior to exposure to study drug are considered pretreatment AEs.

Only TEAEs will be used for tabular summaries and be graded according to the protocol guidelines. Each AE will be assessed for relationship to the study drug and for the rest of the infusion procedure. The duration of all TEAEs in days, from start to end, will be summarized as a numeric variable. Laboratory and vital sign measurements will be evaluated over time using descriptive statistics. Shift analyses of relevant central clinical laboratory parameters will be produced showing shifts from baseline across low, normal, and high categories presented by time point. Descriptive statistics of ECG results and change from baseline at each visit will be presented by treatment group.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}240h}$	area under the curve to 240 hours post dose
AUDIT	Alcohol Use Disorders Identification Test
BMI	body mass index
BP	blood pressure
CBD	cannabidiol
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	confidence interval
CLDQ	Chronic Liver Disease Questionnaire
C_{max}	maximum observed plasma concentration
CP	conditional power
CRO	Contract Research Organization
CSA	clinical study agreement
CSPH	clinically significant portal hypertension
CT	computed tomography
CTP	Child-Turcotte-Pugh
DILI	drug-induced liver injury
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EGD	esophagogastroduodenoscopy
[redacted]	[redacted]
EOS	end of study
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HbA1c	glycated hemoglobin
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency
HRQOL	health-related quality of life
HVPG	hepatic venous pressure gradient
IA	interim analysis
IAC	Interim Analysis Charter
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization

Abbreviation	Definition
IgM	immunoglobulin M
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IWRS	interactive web response system
KM	Kaplan-Meier
LBM	lean body mass
LSM	liver stiffness measurement
MACE	Major Adverse Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
mFAS	modified full analysis set
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PHG	portal hypertensive gastropathy
PK	pharmacokinetic
PPS	per-protocol set
PSS	Patient Safety Services
SAE	serious adverse event
SAF	safety set
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class (MedDRA classification)
SSR	sample size re-estimation
SUSAR	suspected unexpected serious adverse reaction
SV	Screening Visit
$t_{1/2}$	apparent terminal elimination half-life
TBW	total body weight
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
THC	cannabinoids
TIPS	transjugular intrahepatic portosystemic shunts
TLC	Therapeutic Lifestyle Change
TLFB	timeline followback
T_{max}	time of the maximum observed plasma concentration
TSC	Trial Steering Committee
ULN	upper limit of normal
US	United States
VCTE	vibration-controlled transient elastography

1. INTRODUCTION

1.1. Disease Background

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the Western world.[1] The estimated global prevalence of NAFLD is as high as 25%.[2] In the United States (US), approximately 66,000 deaths are due to chronic liver disease each year.[3] The principal risk factors for NAFLD include obesity, and components of the metabolic syndrome, including insulin resistance. NAFLD is characterized by the pathologic accumulation of fat in the liver and has two major histologic phenotypes, fatty liver or non-alcoholic steatohepatitis (NASH).

About 3% to 5% of Americans are affected by NASH.[2] NASH progresses to cirrhosis more frequently than NAFLD[4] and NASH is rapidly rising as an etiology for end-stage liver disease requiring liver transplantation.[5] While the prevalence of cirrhosis in NASH is not clearly defined, as many as one-third of NASH patients progress to advanced fibrosis and/or cirrhosis.[6] The only therapy available to these advanced patients is liver transplantation. NASH has been recognized as a leading causes of cirrhosis in adults in the US, and NASH-related cirrhosis is currently the second most common cause for liver transplants in the US.[7]

Cirrhosis is associated with increased resistance to blood flow through hepatic sinusoids resulting in portal hypertension with increasing collateral blood flow. During the early phases of cirrhosis, portal hypertension has both reversible and irreversible components. As cirrhosis progresses, the reversible component recedes, and portal hypertension becomes fixed. Patients with more pronounced portal hypertension develop a hyperdynamic circulatory state, which in conjunction with increased intrahepatic resistance, maintains the portal hypertensive state and leads to hepatic decompensation events, particularly esophageal varices, variceal bleeding, as well as clinically significant ascites and overt hepatic encephalopathy.

Cirrhosis has two prognostic stages: compensated and decompensated. This staging depends on the absence or presence of clinical complications of cirrhosis (eg, variceal hemorrhages, ascites requiring treatment, or overt encephalopathy). The median survival in the compensated stage exceeds 12 years, whereas it is only 1.8 years in the decompensated stage.[8] The Child-Turcotte-Pugh (CTP) classification is also used to stratify patients, with compensated cirrhotic patients mostly in CTP-Class A, and decompensated cirrhotic patients mostly in CTP-Class B and C.

A challenge in conducting trials for NASH cirrhosis is the correct case definition for inclusion. NASH is a histological diagnosis and yet, as the disease progresses, a significant number of patients with NASHrelated cirrhosis will eventually lack the classic histological findings of NASH at the time of biopsy. That is, even if a liver biopsy is performed, histological findings of cirrhosis often demonstrate "burnt-out" disease evidenced by disappearance of classic histological features of NASH such as steatosis and hepatocyte ballooning. As part of the Liver Forum initiatives, a NASH Cirrhosis Working Group established case definition criteria for attributing NASH as the etiology for cirrhosis. In the present trial (Study GT-031, NAVIGATE), patients with a diagnosis of cirrhosis that also meets the criteria in the first 5 groups defined by the Liver Forum (Appendix 2: 1a, 1b, 1c, 2a, and 2b) will be eligible to participate.

In cirrhosis, clinical signs of portal hypertension reflect increased collateral blood flow, including an enlarged spleen, which traps platelets and thus lowers peripheral platelet counts. Splenic enlargement, and the anatomic changes accompanying increased blood flow in portocollateral vessels (eg, recanalized para-umbilical vein, spleno-renal circulation, and dilated left and short gastric veins) are evaluable by standard imaging methods (eg, magnetic resonance imaging [MRI], computed tomography [CT], and ultrasound). In the present trial (Study GT-031, NAVIGATE), patient eligibility requires clinical evidence of portal hypertension.

The development of esophageal varices and progression to large varices is a harbinger of variceal bleeding, one of the most serious complications of cirrhosis. In patients with compensated cirrhosis, the presence of varices is an important risk factor for death. Bleeding varices cause death in about one third of cirrhotic patients. Once varices develop, the one-year bleeding rate is about 12%, and each bleeding episode is estimated to carry a 6-week mortality of 15% to 20%.[9,10] Due to imminent risk of life-threatening hemorrhage, large varices require clinical intervention.

The development of esophageal varices also heralds other major complications of cirrhosis, including clinically significant ascites and overt encephalopathy. The morbidity and mortality of cirrhosis correlates with 4 stages of increasing disease severity, as categorized by a systematic review of 118 studies that evaluated 23,797 patients.[11] Across these 4 stages, development of esophageal varices impacts survival:

- Stage 1: Absence of both varices and ascites, with approximately 1% annual mortality.
- Stage 2: Presence of varices, but no ascites, with approximately 3.4% annual mortality.
- Stage 3: Presence of ascites with or without varices, and approximately 20% annual mortality.
- Stage 4: Variceal bleed with/without ascites and annual mortality up to 57%.

Epidemiological studies suggest that the development of varices in an individual with compensated cirrhosis is a significant event in the natural history of cirrhosis (transitioning from Stage 1 to Stage 2).[12] Because of its clinical importance, the development of esophageal varices was used as a primary efficacy outcome in a landmark clinical trial of timolol, a non-selective beta blocker, for the prevention of esophageal varices in patients with portal hypertension.[13] Unfortunately, timolol was not effective and at present, no treatments are registered for preventing the formation of varices in compensated cirrhosis.[14]

1.2. Study Rationale

Galectins are a family of proteins, containing 15 members (11 identified in humans), which avidly bind galactose-containing oligosaccharides which constitute the ‘glyco’ component of glycoproteins.[15] The galectin-3 protein is the most widely studied and understood of the galectins and is implicated in the pathogenesis of liver cirrhosis, including the inflammatory and fibrotic processes of NASH. Belapectin (formerly known as GR-MD-02; galactoarabinorhamnogalacturonate) represents- a new therapeutic mechanism for treating patients with advanced fibrosis and/or cirrhosis due to NASH.

Belapectin is a complex carbohydrate derived from a natural plant compound. Belapectin contains oligosaccharide chains and binds to galectin-3, and to a lesser extent, to galectin-1. It has an average molecular weight between [redacted] kDa. Cellular experiments demonstrate that belapectin is not cytotoxic, but inhibits the expression of inflammatory cytokines in a monocyte/macrophage model of inflammation, and also reduces cell surface galectin-3 in fibrogenic stellate cells in the liver. Belapectin's mechanism of action is presumed to be primarily targeting inflammatory hepatic macrophages and subsequently inhibiting the galectin-3 protein which has a role in the pathogenesis of NASH and liver fibrosis.[16]

Belapectin has been tested in 2 animal models of liver fibrosis: a mouse model that reliably reproduces the pathological changes of NASH with fibrosis, and a rat model of thioacetamide-induced liver fibrosis. In the mouse NASH model, belapectin consistently reduced NASH activity, and reduced or eliminated fibrosis (as measured by liver collagen content), and reduced the expression of galectin-3 in liver macrophages.[17] In rats, thioacetamide administration induces a robust fibrosis that replaces about 25% of the liver with collagen, causing the pathological characteristics of cirrhosis. In thioacetamide-induced cirrhotic rats, treatment with 4 weekly doses belapectin reduced liver collagen to below 10%, reversed cirrhosis, and reduced portal hypertension.[18,19]

In a Phase 1 clinical trial of belapectin in patients with advanced hepatic fibrosis (but not cirrhosis), belapectin doses were in the upper range of the targeted therapeutic dose determined from pre-clinical data, and those doses were safe and well-tolerated, with evidence of a pharmacodynamic effect.[19]

A Phase 2 study (GT-026) enrolled 162 patients with portal hypertension (hepatic venous pressure gradient [HVPG] ≥6 mm Hg) and compensated NASH cirrhosis, with administration of belapectin at 2 or 8 mg/kg (lean body mass [LBM]) or placebo every other week for 52 weeks. Belapectin was generally well-tolerated, with no obvious imbalances between treatment groups in treatment-emergent adverse events (TEAEs), adverse events (AEs) with National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or higher, or serious adverse events (SAEs), or cases of drug-induced liver injury (DILI).

In the 54 enrolled patients in the GT-026 study who had mild portal hypertension at baseline (ie, HVPG <10 mm Hg), mean HVPG had increased by 26% in the placebo group, but had decreased in both belapectin groups, by -2%, and -3% in the 2 mg/kg and 8 mg/kg LBM dose groups, respectively, by Week 54. Those differences, compared to placebo treatment, were statistically significant. Considering all 162 patients (HVPG ≥6 mm Hg), a trend toward HVPG benefit (the primary trial efficacy endpoint) with belapectin was observed, but did not attain statistical significance.

In the GT-026 trial, considering only those patients without esophageal varices at baseline (approximately 50% of all patients), the 2 mg/kg LBM belapectin dose had a statistically significant effect to reduce both absolute and percent change in HVPG (both $p = 0.01$). Importantly, *post-hoc* analyses also indicated that patients with no varices at baseline who were administered placebo developed varices at a higher rate than those administered belapectin. Although that trial was not designed with enough patients and statistical power to demonstrate statistically significant differences between belapectin and placebo treatment in the incidence of

new varices, the effect size (18% on placebo vs 0% on belapectin 2 mg/kg LBM) was of noticeable clinical interest.

In the GT-026 trial, the evaluation of liver biopsy data indicated a significant reduction of hepatocyte ballooning (reflecting hepatocyte death) with the belapectin 2 mg/kg LBM dose level, and a strong trend with the belapectin 8 mg/kg LBM dose level, compared to placebo.

Taken together, the prior trial data support evaluating the primary hypothesis of the present trial: that belapectin will reduce the incidence of new varices in patients with NASH cirrhosis who have not yet developed esophageal varices.

The pharmacokinetic (PK), efficacy and safety results from the prior GT-026 Phase 2 study in patients with NASH cirrhosis also supports evaluating belapectin doses of 2 mg/kg or 4 mg/kg LBM every 2 weeks, as further described in Section 3.4.

A drug-drug interaction trial with belapectin and midazolam demonstrated no effect on the PK of midazolam. Additional exploratory, openlabel trials in other diseases - specifically plaque psoriasis, atopic dermatitis, melanoma and in combined immunotherapy for advanced melanoma, and head and neck cancer - indicate that belapectin also appeared safe and well tolerated in these patients' populations.

Based on accumulated safety and efficacy data from previous clinical trials, the present trial has been designed to evaluate belapectin in patients with NASH cirrhosis without esophageal varices at baseline. By reducing the formation of new varices and thereby slowing the progression of liver cirrhosis and portal hypertension, belapectin is also hypothesized to ultimately improve other clinical outcomes such as variceal bleeds, ascites, encephalopathy, and need for liver transplantation.

1.3. Benefit-risk Assessment

Consistent with pre-clinical toxicology and safety pharmacology studies, the clinical safety data from completed Phase 1 and Phase 2 trials in NASH patients show no obvious imbalances between belapectin and placebo control groups in the incidence, nature or severity of TEAEs, AEs classified as Grade 3 or higher, or SAEs. In the 52 week GT-026 Phase 2 study in NASH patients, 2% (nasal congestion, pruritus, headache, rash) of all AEs in belapectin treated patients were judged by the Investigator to be probably related to belapectin, and 0.2% (musculoskeletal stiffness Grade 1) were judged as definitely related to belapectin.

Belapectin may have meaningful therapeutic benefit in NASH cirrhosis, based on the robust efficacy in pre-clinical NASH animal models, and the Phase 2 trial data that are consistent, in compensated cirrhotic NASH patients without varices, with reducing both HVPG and the development of new varices.[20]

Preventing the development of new esophageal varices and their progression to large varices would reduce the risk of life-threatening variceal hemorrhage. In cirrhotic patients, the rate of bleeding from varices is approximately 12% at 2 years, and the 6-week mortality rate among patients with variceal bleeding is approximately 20%. By slowing the progression of liver cirrhosis through its anti-fibrotic mechanism of action, belapectin treatment is expected to not

only reduce the incidence of new varices, but also reduce the incidence of other cirrhosis-related outcomes (eg, variceal bleeding, ascites, hepatic encephalopathy, liver transplant, and liver-related mortality) that contribute to the morbidity and mortality of NASH cirrhosis.

The risks to patients in this trial are related to standard clinical diagnostic procedures, including esophagogastroduodenoscopy (EGD). For each patient, EGD exams will be performed at baseline, at the end of Phase 2b (Week 78, 18 months) and at the end of Phase 3 (Week 78, 18 months; Section 7.2.1.4). Hence, patients enrolled at the Phase 2b stage will have 3 endoscopies and patients enrolled at the Phase 3 stage will have 2 endoscopies. In addition, patients who discontinue early will have an EGD performed at Early Termination Visit regardless of which visit or phase the discontinuation occurs. These EGD intervals are consistent with recommended standard of care practice for patients with compensated cirrhosis.

The complications of EGD include those related to sedation, complications related to the endoscopy, and complications related to diagnostic and therapeutic maneuvers.[21] Data are limited regarding the overall risk of complications but in a large survey from 1974 that was based upon 200,000 upper endoscopies, the overall complication rate was 0.13%, and the mortality rate was 0.004%. Subsequent studies have estimated EGD complication rates of 0.15% overall, and 0.0002% for diagnostic endoscopy without therapeutic maneuvers,[22] as in the present study.

The most frequent and serious complications of procedural sedation are cardiopulmonary. In the general population, risk factors for cardiopulmonary complications include advanced age, underlying comorbid illness (especially pulmonary disease), dementia, anemia, obesity, and endoscopy performed for emergent indications.[23] Adverse events resulting from oversedation include hypoxemia, hypoventilation, airway obstruction, hypotension, vasovagal episodes, arrhythmias, and aspiration. In the present belapectin trial, all EGDs will be performed by experienced gastroenterologists, under carefully controlled, non-emergent conditions, without therapeutic intent, and in a highly selected patient population that generally will lack the aforementioned risk factors for cardiopulmonary complications.

The cirrhotic patients in this trial will obtain the benefit of periodic EGD screening for new varices, and may receive standard of care treatment as warranted (eg, treatment with non-selective beta blockers, or variceal ligation) according to professional medical society guidelines.

Patients screening for this trial will have either already had a liver biopsy (as part of prior medical evaluations), or will undergo a single baseline liver biopsy - to confirm that the diagnosis of NASH cirrhosis meets the protocol-specified inclusion criteria. No additional liver biopsies are planned.

Pain is the most common complication following liver biopsy, with approximately one-fourth of patients experiencing pain in the right upper quadrant or right shoulder. The pain is usually dull, worse with inspiration, mild, and resolves completely within a few hours.

The most common serious complication of the liver biopsy procedure is intraperitoneal hemorrhage, although hematoma and hemobilia can also occur. Severe bleeding resulting in

hemodynamic compromise or requiring intervention has been reported following 0.01% to 0.5% of liver biopsies.[24] In over 6,600 image-guided liver biopsies, the incidence of hematoma requiring transfusion or angiographic intervention was reported as 0.5%.[24]

Serious complications following liver biopsy was reported at approximately 1% in two series that included 3000 to 6000 patients,[25,24] while in another analysis of over 60,000 patients, overall mortality risk was estimated at 0.2%.[26] Sixty percent of complications occur within 2 hours of the procedure, and in two studies including 6000 to 68,000 patients, 83% to 96% of complications occurred within 24 hours.[27,24] Approximately 2% to 3% of patients require hospital admission for management of complications; pain or hypotension are the predominant causes.[23,28]

For a patient being screened for participation in this trial, obtaining a baseline liver biopsy would occur if needed, only after the other screening evaluations are completed and are deemed satisfactory.

More detailed information about the known and expected benefits and risks and reasonably expected AEs are found in the belapectin Investigator's Brochure (IB).

2. OBJECTIVES AND ENDPOINTS

In this seamless, adaptive, two-stage Phase 2b/3 trial in patients with NASH cirrhosis and clinical signs of portal hypertension but without esophageal varices at baseline, an interim analysis (IA) will occur during Stage 1 of this trial (Phase 2b, after 78 weeks [18 months] of treatment), and then following any adaptive modifications based on that IA, the trial will continue seamlessly into Stage 2 (Phase 3, also with 78 weeks [18 months] of treatment).

The objectives and endpoints for Phase 2b and Phase 3 are stated below. Endpoints are applied independently to 2 groups of patients: patients that enter at the beginning of Stage 1 (Phase 2b) and continue through to the end of Stage 2 (Phase 3) (for a total of 156 weeks [36 months] of participation), and new patients that are randomized only into Stage 2 (Phase 3) (for a total of 78 weeks [18 months] of participation).

Objectives	**Endpoints**
Primary Efficacy Objective	**Primary Efficacy Endpoint**
To evaluate the efficacy of 2 mg/kg and 4 mg/kg LBM of belapectin compared to placebo in preventing the development of esophageal varices	Proportion of patients in the belapectin treatment groups who develop esophageal varices at 78 weeks [18 months] of treatment compared to placebo
Key Secondary Efficacy Objective	**Key Secondary Efficacy Endpoint**
To evaluate effect of belapectin on composite clinical outcomes	Incidence rate of patients in the belapectin treatment groups, compared to placebo, who develop any of the following: 1) varices (esophageal or gastric) requiring treatment, 2) variceal bleed requiring hospitalization, 3) clinically significant ascites requiring hospitalization, 4) spontaneous bacterial peritonitis, 5) overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization), 6) mortality (all-cause), 7) liver transplant, 8) model for end-stage liver disease (MELD) score ≥15 on 2 consecutive occasions.
Additional Secondary Efficacy Objectives	**Additional Secondary Efficacy Endpoints**
To evaluate effect of belapectin on progression of esophageal varices	Incidence rate of patients in the belapectin Phase 3 treatment group who progress to large esophageal varices or develop red wales compared to placebo.
To evaluate effect of belapectin treatment on liver cirrhosis-related clinical events	Event-free survival by time to first cirrhosis-related clinical event, including the following: • progression to large varices or red wales • esophageal variceal hemorrhage requiring hospitalization • clinically significant ascites requiring hospitalization • spontaneous bacterial peritonitis

Objectives	Endpoints
	• overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization) • CTP score increase of ≥2 points (from baseline) as measured on 2 consecutive occasions • MELD score increase to ≥15 as measured on 2 consecutive occasions • liver transplant • liver-related death
Exploratory Efficacy Objectives	**Exploratory Efficacy Endpoints**
To evaluate the effect of belapectin compared to placebo on liver fibrosis	Change in liver stiffness measurement (LSM), baseline-adjusted, as determined by vibration-controlled transient elastography (VCTE) (FibroScan) exams during Phase 2b and Phase 3
To evaluate the effect of belapectin compared to placebo on portal hypertensive gastropathy (PHG)	• Difference in development of PHG between belapectin treated and placebo patients • Difference in resolution or improvement in PHG between belapectin treated and placebo patients
To assess the effect of belapectin compared to placebo on health-related quality of life (HRQOL)	Difference in Chronic Liver Disease Questionnaire (CLDQ) scores between belapectin and placebo treatment during Phase 2b and Phase 3
Safety Objectives	**Safety Endpoints**
To assess the safety and tolerability of belapectin compared to placebo treatment	The safety endpoints include: • incidence and nature of AEs, including adjudicated DILI and adjudicated cardiovascular events (Major Adverse Cardiac Event [MACE]) • changes from baseline in physical examinations, vital signs, and electrocardiogram (ECG) parameters • changes from baseline in routine central laboratory tests (clinical chemistry, hematology), including liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transferase [GGT], alkaline phosphatase [ALP]), and liver function markers (bilirubin, albumin, international normalized ration [INR])
PK Objective	**PK Endpoint**
To produce a population PK model of belapectin	Plasma belapectin concentrations and PK parameters (area under the curve [AUC], maximum observed plasma concentration [C_{max}], time of the maximum observed plasma

Objectives	Endpoints
	concentration [T_{max}], apparent terminal elimination half life [$t_{1/2}$]) in Phase 2b (a minimum of 30 patients per treatment group) and in Phase 3 (a minimum of 30 patients per treatment group).

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

This seamless, adaptive, two-stage, Phase 2b/3, randomized, double-blind, multicenter, parallel-groups, placebo-controlled study will assess the efficacy, safety, and tolerability of belapectin compared with placebo in patients with NASH cirrhosis (Appendix 2) and clinical signs of portal hypertension but without esophageal varices at baseline.

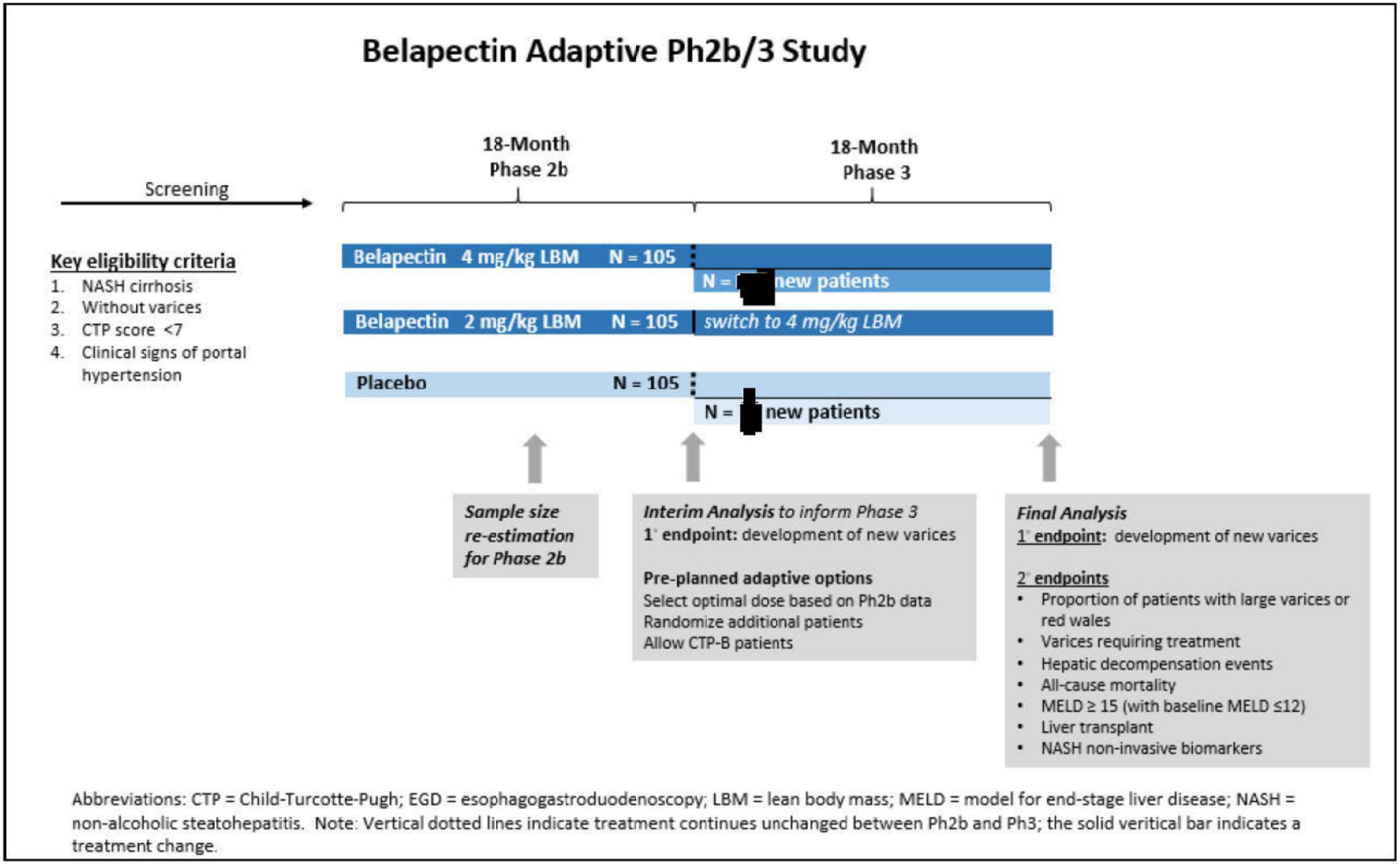
In the first stage of this trial, Phase 2b, approximately 315 patients will be randomized in a 1:1:1 ratio (105 patients per group) to belapectin 2 mg/kg LBM or belapectin 4 mg/kg LBM or placebo, administered intravenously (IV) every other week for 78 weeks (18 months). During Phase 2b, a non-comparative (blinded) sample size re-estimation (SSR) procedure will be conducted when at least 50% of patients complete 78 weeks (18 months) of Phase 2b treatment, to confirm initial sample size assumptions. Additional patients may then be enrolled in Phase 2b, up to a maximum of 65 additional patients in each Phase 2b treatment group, without requiring a protocol amendment. When all enrolled patients in Phase 2b (Stage 1) have completed 78 weeks (18 months) of treatment, an IA will occur to select the optimal belapectin dose and to confirm the patient sample size for the second stage, Phase 3. The IA could also lead to termination of the study (per pre-specified criteria defined in the Statistical Analysis Plan [SAP]). An independent Data Safety Monitoring Board (DSMB) will oversee the IA and make recommendations on adaptive modifications to an independent Trial Steering Committee (TSC). The IA and potential study adaptations, including SSR procedures, are summarized in this protocol and outlined in detail in the SAP. The DSMB will follow procedures detailed in the separate DSMB Charter, to ensure study integrity.

Patients who complete Phase 2b will continue into Phase 3 for 78 additional weeks (18 additional months), to continue treatment with belapectin (at the same or a modified dose*) or to continue treatment with placebo. For patients who start Phase 3 prior to IA, they will similarly continue on their current treatment until IA and may be switched to a modified dose based on the results of the IA. Patients who switch to the optimal belapectin dose will be analyzed separately. [*For example, if the 4-mg/kg LBM dose was chosen at the IA as the optimal dose for evaluation in Phase 3, then the patients who received the 2-mg/kg LBM dose in Phase 2b will be switched to the 4-mg/kg LBM dose for the remainder of their Phase 3 participation.] Phase 3 has a parallel-groups design with 78 weeks (18 months) of treatment, comparing one optimal dose level of belapectin to placebo. Approximately 210 additional patients will be enrolled directly into Phase 3, in a 2:1 ratio to the optimal belapectin dose (approximately [redacted] patients) or placebo (approximately [redacted] patients), respectively. However, contingent on IA results, a total of up to [redacted] ([redacted] additional patients could be enrolled directly in Phase 3, without requiring a protocol amendment.

Study Periods:

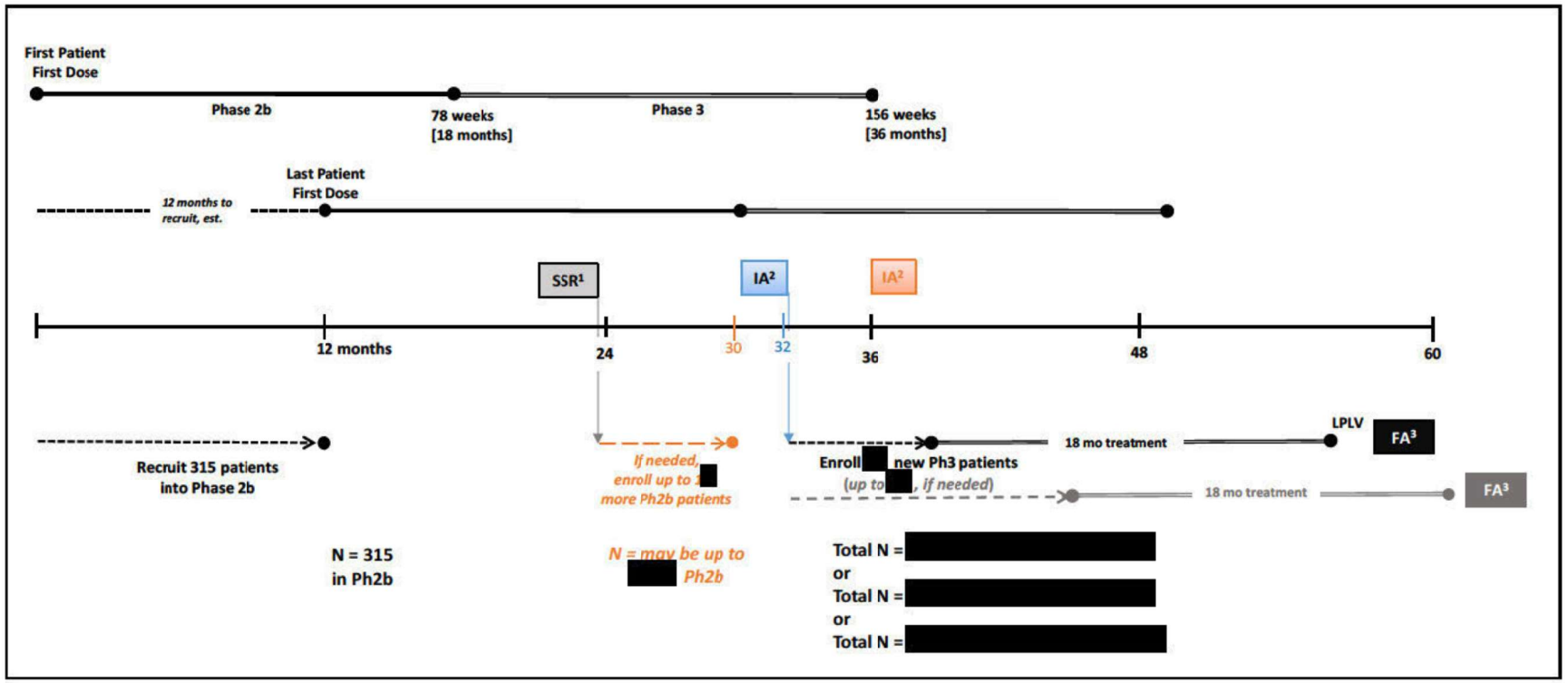
The study is comprised of a Phase 2b (Stage 1) and Phase 3 (Stage 2), as shown in Figure 1 and Figure 2, below. All procedures to be conducted during these periods are detailed in Appendix 5.

Figure 1: Study Design



Abbreviations: CTP = Child-Turcotte-Pugh; EGD = esophagogastroduodenoscopy; LBM = lean body mass; MELD = model for end-stage liver disease; NASH = non-alcoholic steatohepatitis. Note: Vertical dotted lines indicate treatment continues unchanged between Ph2b and Ph3; the solid veritical bar indicates a treatment change.

Figure 2: Study Timelines



1. **SSR** = Sample size re-estimation; when 5 % of Ph2b patients complete 18 months. Up to additional patients *may* be added to each Ph2b arm, which *could* require about 6 months to recruit. If (= additional patients are enrolled, then the total N = (= patients would be enrolled in Phase 2b.
2. **IA** = Interim analysis; when all Ph2b patients complete 18 months. IA decisions include: go/no-go to Ph3, and Ph3 patient N. IA is to occur at about month 30. The IA *may* occur later, if up to more patients are to be enrolled in Ph2b after the SSR.
3. **FA** = Final analysis; after Ph3 LPLV (last patient last visit). FA may occur later, if up to more patients are enrolled after the SSR and/or if up to new Ph3 patients are enrolled after the IA.

Stage 1: Phase 2b

Identification of Patients: Prior to signing the informed consent, potential patients will be identified as per local standard of care for a diagnosis of NASH cirrhosis (including a historic liver biopsy, if available), and presence or absence of esophageal varices (based on historic EGD, if available).

Screening (Week -10 to Day -1): Following the signing of the informed consent, assessments for eligibility (by inclusion and exclusion criteria) will occur within 10 weeks (2.5 months) before randomization, as follows:

- Medical, surgical and medication history, vital signs (heart and respiratory rate, blood pressure [BP] and body temperature), complete physical examination, including height and weight, ECG, and central clinical laboratory evaluations (hematology, chemistry, coagulation profile, urinalysis, specialized tests for specific liver diseases, and pregnancy test [for women of childbearing potential]).

- Clinical signs of portal hypertension, with either one of the following: (a) platelet count <150,000/mm^3 (from central laboratory or historical record, such as detailed chart notes providing platelet numbers or copies of laboratory reports showing platelet count[s] below 150,000/mm^3) or (b) documented HVPG measurement >6 mmHg

  OR

  (c) at least two of the following: spleen size ≥14 cm by imaging (ultrasound, MRI, or CT scan), evidence of abdominal collateral circulation (by ultrasound, MRI, or CT scan or caput medusae seen upon physical examination), or documented liver transient elastography (eg, FibroScan) ≥20 kPa or AST/ALT >1.

- EGD with video recording documentation to confirm the presence or absence of esophageal varices.

- Liver and abdomen ultrasound exam, to screen for hepatocellular carcinoma (HCC) and for ascites.

- Liver biopsy, while not required, can be used to confirm diagnosis of NASH cirrhosis by the central study pathologist, if necessary. (A historic liver biopsy is acceptable but the biopsy blocks and/or slides must be available for central review if this is the main/only confirmation being used for evidence of NASH cirrhosis.) Results from the central study pathologist must be available before the patient is randomized.

Note: It is not required for all of the assessments above to be performed on the same day. All appropriate steps should be taken to ensure study-related assessments are completed and results available within the 10-week screening period, with the exception of delays in laboratory results (including biopsy) and EGD reporting which were not due to site delays in performing these examinations.

Randomization/Treatment (78 Weeks [18 months]): Patients meeting all inclusion and no exclusion criteria will be randomized (1:1:1) to 1 of 3 treatments: placebo, belapectin 2 mg/kg or 4 mg/kg LBM, administered IV every other week for 78 weeks (18 months). Randomized patients will be stratified by type 2 diabetes status.

During the treatment period, efficacy, safety, tolerability, and PK will be assessed as indicated in Appendix 5.

Patients who complete Phase 2b (Stage 1) will continue into Phase 3 (Stage 2), to continue belapectin treatment (at the same or a modified dose) or continue treatment with placebo. For patients who start Phase 3 prior to IA, they will similarly continue on their current treatment until IA and may be switched to a modified dose based on the results of the IA.

The following efficacy assessments will be performed:

- EGD with video recording documentation, to assess varices at the end of Phase 2b (Week 78) or upon early discontinuation at any visit. An independent endoscopy review expert panel will review all EGD records (including the baseline EGD), and adjudicate all assessments.
- Transient elastography (eg, FibroScan) to assess liver stiffness, at approximately 6 month intervals.
- Blood samples for liver enzymes (eg, ALT, AST, ALP, GGT) and liver function markers (eg, bilirubin, albumin, INR) and platelet counts will also be drawn periodically, together with routine central clinical laboratory tests for safety monitoring during planned study center visits, as indicated in the protocol Schedule of Assessments.
- At the start and end of Phase 2b, blood samples will be stored (-80°C) for other possible post-study biomarker tests and gene expression analysis.

Early Termination Visit and End of Study Visit: Patients who discontinue Phase 2b early (prior to Week 78) will have an Early Termination Visit (14 to 28 days after their last dose) as well as an End of Study (EOS) Visit (14 days after the Early Termination Visit), and will not be eligible to participate in Phase 3. Assessments during these visits will be carried out as indicated in Appendix 5.

Interim Analysis

A pre-specified IA of efficacy and safety data will be conducted after all planned patients in Phase 2b (Stage 1) have completed 78 weeks (18 months) of treatment (see Section 3.1.1). The purpose of the IA is to allow potential adaptive modifications of the study, including: (1) select the optimal dose of belapectin for Phase 3 (Stage 2), (2) re-estimate the patient sample size for Phase 3, (3) re-evaluate the treatment allocation ratio for Phase 3, (4) re-evaluate the inclusion and exclusion criteria for Phase 3, including the CTP status, (5) and/or terminate the study. The IA and dose selection as well as sample size and decision rules are further described in Section 3.1.1 and Section 3.1.2, respectively.

An Interim Analysis Charter will specify the membership and roles of an independent DSMB and TSC, the IAs adaptive rules and decision criteria that define potential modifications of the study, and the operational procedures to preserve study blinding and integrity.

Stage 2: Phase 3

Identification of new patients entering Phase 3: Prior to signing the informed consent, potential patients will be identified per local standard of care for a diagnosis of NASH cirrhosis (including a historic liver biopsy, if available), and presence or absence of esophageal varices (based on historic EGD, if available).

Screening: Following the signing of the informed consent, assessments for eligibility (by inclusion and exclusion criteria) will occur within 10 weeks (2.5 months) before randomization, as follows:

- Medical, surgical and medication history, vital signs (heart and respiratory rate, BP, and body temperature), complete physical examination, including height and weight, ECG, and central clinical laboratory evaluations (hematology, chemistry, coagulation profile, urinalysis, specialized testing for specific liver diseases, and pregnancy test [for women of childbearing potential]).

- Clinical signs of portal hypertension, with either one of the following: (a) platelet count <150,000/mm^3 (central laboratory or historical record, such as detailed chart notes providing platelet numbers or copies of laboratory reports showing platelet count[s] below 150,000/mm^3) or (b) documented HVPG measurement >6 mmHg

  OR

  (c) at least two of the following: spleen size ≥14 cm by imaging (by ultrasound, MRI, or CT scan), evidence of abdominal collateral circulation (by ultrasound, MRI, or CT scan or caput medusae seen upon physical examination), or documented liver transient elastography (eg, FibroScan) ≥20 kPa or AST/ALT >1.

- EGD with video recording documentation to assess the absence/presence of esophageal varices.

- Liver and abdomen ultrasound exam, to screen for HCC and for ascites.

- Liver biopsy, while not required, can be used to confirm diagnosis of NASH cirrhosis by the central study pathologist, if necessary. (A historic liver biopsy is acceptable but the biopsy blocks and/or slides must be available for central review if this is the main/only confirmation being used for evidence of NASH cirrhosis.) Results from the central study pathologist must be available before the patient is randomized.

Note: It is not required for all of the assessments above to be performed on the same day. All appropriate steps should be taken to ensure study-related assessments are completed and results available within the 10-week screening period, with the exception of delays in laboratory results

(including biopsy) and EGD reporting which were not due to site delays in performing these examinations.

Treatment Phase (78 Weeks [18 months]): Patients meeting all inclusion and no exclusion criteria will be randomized in a 2:1 ratio to either belapectin (the optimal dose, either 2 mg/kg or 4 mg/kg LBM) or placebo, dosed every other week for 78 weeks (18 months).

During the treatment period, efficacy, safety, tolerability, and PK will be assessed as indicated in Appendix 5.

The following efficacy assessments will be performed:

- EGD with video documentation, to assess varices at the end of Phase 3 or upon early discontinuation at any visit. An independent endoscopy review expert panel will review all EGD records (including the baseline EGD), and adjudicate all assessments.
- Transient elastography (eg, FibroScan) to assess liver stiffness, approximately every 6 months
- Blood samples for liver enzymes (eg ALT, AST, ALP, GGT) and liver function tests (eg, bilirubin, albumin, INR) and platelet counts will also be drawn periodically, together with routine central clinical laboratory tests for safety monitoring during scheduled study center visits, as indicated in the protocol Schedule of Assessments.
- At the start (for newly-enrolled patients) and end of Phase 3, and at time points indicated in the schedule of assessments, a blood sample will be stored (-80°C) for other possible post-study biomarker tests and gene expression analysis.

Early Termination Visit and End of Study Visit: Patients who discontinue Phase 3 early will have an Early Termination Visit (14 to 28 days after their last dose) as well as an EOS Visit (14 days after the Early Termination Visit).

Patients who complete Phase 3 will have an End of Treatment Visit (14 to 28 days after their last dose) as well as an EOS Visit (14 days after the End of Treatment Visit).

Assessments during these visits will be carried out as indicated in Appendix 5.

3.1.1. Interim Analysis

At the IA, the following decisions will be considered by the DSMB, based on a comparative analysis of efficacy and safety data:

- Terminate the trial due to overwhelming efficacy, due to futility (see Conditional Power rule in Section 3.1.2), or due to safety concerns.
- Select the optimal belapectin dose level for Phase 3 (either 2 or 4-mg/kg LBM, IV, every other week).

- Continue the trial and maintain or increase the number of patients to be enrolled in Stage 2 (Phase 3) to reach the planned study power for the primary efficacy endpoint analysis.

The analysis of interim data for the primary endpoint will be performed by an independent unblinded data analysis group (Fortrea) that is not affiliated with the Sponsor (Galectin). A DSMB will review the IA results for Phase 2b and provide final recommendations to the independent TSC regarding trial termination and adjustment of the target number of patients for Phase 3. A detailed description of the IA procedures and decision-making process will be provided in the DSMB Charter.

3.1.2. Sample Size and Decision Rules

The EAST software (version 6.5, Cytel) will be used for the adaptive trial initial sample size estimations, and the sample size re-estimations, and the IA. The multi-arm, multi-stage module (of the EAST software) with p-value combination method will be used for the adaptive design.

Initial Patient Sample Size Estimates

Based on the GT-026 belapectin trial, we assume the annual incidence rate is [redacted]% for patients to develop new esophageal varices in the placebo treatment group and is [redacted]% for the belapectin 2 mg/kg LBM or 4 mg/kg LBM group (ie, [redacted]% risk reduction compared to placebo treatment). Derived from the annual incidence rates, the proportion of patients developing new esophageal varices at 78 weeks (18 months) are [redacted]% for placebo and [redacted]% for either the belapectin 2 mg/kg LBM or 4 mg/kg LBM groups. The risk reduction from placebo treatment at 78 weeks (18 months) [redacted]%.

For estimating the patient sample size for the primary efficacy endpoint (the incidence of new varices at 78 weeks [18 months]), the following assumptions were made:

1. The proportion of patients developing esophageal varices in the placebo group at 78 weeks [18 months] will be [redacted]%
2. The proportion of patients developing esophageal varices on belapectin (either 2 mg/kg LBM or 4 mg/kg LBM) at 78 weeks [18 months] will be [redacted]%
3. Significance level (Type I error) alpha = [redacted]
4. The efficacy boundary: Adjusted p-value = [redacted]
5. The randomization ratio for Stage 1 (Phase 2b) is 1:1:1 for 2 mg/kg LBM, 4 mg/kg LBM, and placebo groups, respectively. The randomization ratio for Stage 2 (Phase 3) is 2:1 for the selected optimal belapectin dose and placebo, respectively.
6. Information fraction at the IA = [redacted]

Based on the assumptions above, a total patient sample size of [redacted] will provide at least [redacted]% power for demonstrating that either the belapectin 2 mg/kg LBM or 4 mg/kg LBM treatment is

superior to placebo with respect to the primary efficacy endpoint for this Phase 2b/3 study. For Phase 2b, [redacted] patients would be needed in each of the 3 treatment groups. For Phase 3, [redacted] additional new patients would need to be enrolled: [redacted] patients in the optimal belapectin dose group and [redacted] in the placebo group. The Bonferroni method for multiplicity adjustment is used to compute the adjusted p-value (p-value corresponding to the global NULL).

Additionally, to account for an anticipated rate of patient withdrawal or discontinuation during the study of about [redacted]% in Phase 2b and similarly about [redacted]% in Phase 3, a total of [redacted] patients need to be enrolled to reach the required sample size of [redacted], including about [redacted] patients in each of the 3 treatment groups in Phase 2b and about [redacted] additional new patients in Phase 3 ([redacted] patients in the optimal belapectin dose group and [redacted] patients in the placebo group).

During Stage 1 (Phase 2b), a non-comparative SSR procedure (blinded to study staff and patients) will be done to confirm the incidence rate of patients developing new esophageal varices that was assumed for the initial sample size calculation. This sample size re-estimation will be done when at least [redacted]% of Phase 2b patients have completed 78 weeks (18 months) of treatment. This sample size re-estimation in Phase 2b will not affect the overall Type I error since it is based on non-comparative data. If the sample size is increased in Phase 2b, the sample size for the overall study will be increased accordingly. The IA that occurs at the end of Phase 2b (when all patients in Phase 2b have completed 78 weeks [18 months] of treatment), will be done with the same information fraction ([redacted]%) as planned, based on the new total sample size.

Interim Analysis Decision Rules and Sample Size Re-estimation

For the IA decision rules, the conditional power (CP) method will be used together with the best treatment selection. CP will be evaluated at the IA, ie, the probability of establishing a significant treatment effect on the primary efficacy endpoint at the planned final trial analysis (ie, at the end of Phase 3), conditional upon the primary efficacy endpoint data available at the IA. That CP will be calculated under the assumption that the true underlying treatment difference in Stage 2 (Phase 3) is equal to the treatment difference computed at the time of the IA.

The trial's design may be modified at the IA, using the following rules:

- If there are major safety concerns, stop the trial;
- If at least one of the null hypotheses corresponding to the comparisons of the belapectin doses versus placebo can be rejected using the closed testing approach at IA using the alpha-level [redacted] for the comparison of primary efficacy, stop the trial for efficacy;
- Otherwise, the following CP rules will apply:
  - If CP < [redacted] (Futility/Unfavorable zone), stop the trial after IA for futility;
  - If [redacted] ≤ CP < [redacted] (Promising zone), the independent DSMB will discuss and make recommendations on adaptive modifications to the TSC to stop or continue the trial. If patient sample sizes are increased, the target number of patients will be increased to achieve a nominal study power of [redacted]%;
  - If CP ≥ [redacted] (Favorable zone), continue the trial to the planned final analysis with the original target number of patients.

3.2. Discussion of Study Design, Including the Choice of Control Groups

The development of new esophageal varices in patients with hepatic cirrhosis precedes the development of larger varices that may bleed – with significant morbidity and mortality. Bleeding varices are a cause of death in about one-third of cirrhotic patients.

The development of new varices reflects the progression of hepatic cirrhosis and thus also portends the development of later complications such as significant ascites, hepatic encephalopathy, and eventual liver failure. The incidence of new varices will be assessed by adjudicated EGD visualization, performed at intervals that are consistent with recommended "standard of care" clinical monitoring guidelines (refer to the EGD Charter for this study).

This trial in compensated NASH cirrhosis patients is designed to determine if belapectin treatment significantly reduces the rate of development of new varices (the primary efficacy endpoint), but will also assess whether belapectin treatment reduces the longer term incidence of major adverse sequelae of NASH cirrhosis, ie components of the key secondary efficacy composite endpoint including: varices (esophageal or gastric) requiring treatment, variceal bleeds requiring hospitalization, clinically significant ascites requiring hospitalization, bacterial peritonitis, hepatic encephalopathy requiring hospitalization, liver transplant, and death.

The first stage of this trial (Phase 2b), will evaluate the efficacy of two dose levels of belapectin with treatment for 78 weeks (18 months). The optimal belapectin dose level, balancing safety and efficacy, is currently uncertain – although doses up to 8 mg/kg LBM every 2 weeks for up to 52 weeks were assessed as safe and well tolerated in the prior belapectin Phase 2 trial (Study GT-026) in patients with NASH cirrhosis. The 78 week (18 month) treatment duration in the first stage (Phase 2b) of the present trial is estimated to be sufficient for the overall trial with the planned number of enrolled patients (Phase 2b + Phase 3) to detect (with [redacted]% power, and 1-sided significance level of 0.025) a clinically meaningful treatment effect of belapectin on the incidence of new varices (ie, [redacted]% relative risk reduction at 78 weeks [18 months], compared to placebo).

However, if the incidence rate of new varices is lower than initially anticipated, then the overall trial might be under-powered, and could yield a false negative result. To avoid that possibility, Phase 2b incorporates a non-comparative blinded SSR procedure (occurring when at least 50% of patients complete 78 weeks [18 months] of Phase 2b treatment). If the incidence rate of new varices during that SSR is less than that initially assumed, then additional patients may be enrolled into Phase 2b (without requiring an amendment, a maximum of [redacted] additional patients may be enrolled in each of the three Phase 2b treatment arms), to ensure adequate trial power.

However, the 78 weeks (18 months) duration of Phase 2b is possibly too short for confirming potential effects of belapectin on the incidence of long-term cirrhosis-related clinical outcomes (ie, the clinical events that comprise the key secondary efficacy composite endpoint). Therefore, the patients enrolled in Phase 2b will continue treatment (belapectin or placebo) during the 78 weeks (18 months) of Phase 3, and continue all efficacy and safety assessments. As well, [redacted] additional new patients are also planned for enrollment directly into Phase 3, to provide a total patient sample size sufficient for this trial to obtain at least [redacted]% power for assessing the primary efficacy endpoint, and to provide a reasonable patient sample size for evaluating the key

secondary efficacy (composite) endpoint, and also to provide a suitably large patient safety experience data base for pivotal regulatory reviews. Compared to conducting a Phase 2b trial, followed by a separate Phase 3 trial, this seamless, adaptive two-stage Phase 2b/3 trial design reduces the total number of patients required, maximizes the potential for an individual patient to receive therapeutic benefit, and is an expeditious route for obtaining the critical efficacy and safety data required for regulatory evaluation of belapectin.

When all patients enrolled in Phase 2b have completed 78 weeks (18 months) of treatment, a formal, unblinded (comparative) IA will be performed, to determine if the trial should be stopped (for efficacy, safety, or futility), should proceed as planned, or should proceed but with a somewhat higher number of new patients enrolled into Phase 3 to ensure adequate study power for the primary efficacy endpoint. The IA will be conducted by the DSMB, without involvement of the clinical study team or study investigators or Sponsor, according to a detailed DSMB Charter, that pre-specifies the roles and responsibilities of the DSMB members, provides operational procedures to maintain blinding and ensure study integrity, and also specifies the adaptive trial decision rules and allowable adaptive trial modifications.

The IA will also be used to choose the optimal dose level of belapectin (either 2 mg/kg or 4 mg/kg LBM IV every 2 weeks) for use in Phase 3, based on analysis of all accumulated safety and efficacy data from Phase 2b. After the IA, those patients who had received the discontinued belapectin dose during Phase 2b will be switched to the optimal belapectin dose for continued treatment during Phase 3; the final efficacy and safety data from that "switched-dose" group of patients will be analyzed as a subset, distinguished from the patients who received only the final Phase 3 dose level of belapectin throughout the entire trial. For patients who start Phase 3 prior to the IA, they will continue on their current treatment until IA and may be switched to a modified dose based on the results of the IA.

The IA will also determine whether patients with a greater degree of cirrhosis severity may be enrolled into Phase 3. The trial protocol (currently) excludes patients with a CTP score of 7 or above, since prior clinical PK data has indicated that plasma belapectin exposures are somewhat higher in patients with higher levels of hepatic impairment. Based on the safety and PK data from Phase 2b, as well as pending PK and safety results from a separate trial of belapectin in patients with hepatic impairment that is ongoing (Study GT-032) and is expected to be completed prior to the IA, the DSMB can recommend whether to allow enrollment of NASH cirrhosis patients with CTP scores ≥7, which would expand the potential patient population that might eventually be prescribed belapectin therapy.

Since no drugs are currently available for preventing the development of new varices or for slowing the progression to the late clinical sequelae of NASH cirrhosis, placebo use in this study is considered an acceptable comparator for the prevention of esophageal varices in patients with NASH cirrhosis and clinically significant portal hypertension (CSPH).

Inclusion of patients with clinical signs of portal hypertension in this trial is based on screening measurements of spleen diameter (assessed as spleen bipolar diameter crossing the spleen hilium) and platelet count.[15] In one study[29] in 117 patients with compensated cirrhosis with measurement of HVPG (training set), the mean ± standard deviation (SD) spleen size, measured by ultrasound, in patients with CSPH was 13.9 cm ± 3.1 cm compared to the patients without

CSPH who had a mean ± SD spleen size of 11.5 cm ± 2.1 cm. Therefore, the inclusion criteria for spleen size in the present belapectin trial use a threshold cutoff value of 14.0 cm.

3.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the study (end of Phase 3, Stage 2).

3.4. Selection of Belapectin Doses

[redacted]

4. SELECTION OF STUDY POPULATION

A total of approximately 525 patients, including 315 patients in Phase 2b (Stage 1) and [redacted] patients in Phase 3 (Stage 2), will be enrolled in approximately 150 study centers in the US, Europe, and international locations. Patients will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is generally not permitted.

4.1. Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Is male or female, ≥18 and ≤75 years of age at the time of Screening.

2. Is willing and able to provide written informed consent prior to the initiation of any study-specific procedures.

3. Has evidence of portal hypertension, with either one of the following:
    a. platelet count <150,000/mm^3 (from central laboratory or historical record, such as detailed chart notes providing platelet numbers or copies of laboratory reports showing platelet count[s] below 150,000/mm^3)

    OR

    b. documented HVPG measurement >6 mmHg

    OR

    c. at least two of the following:
        - spleen size ≥14 cm (documented by ultrasound, MRI, or CT scan)
        - abdominal collateral circulation (documented by ultrasound, MRI, or CT scan or physical examination, ie, caput medusae)
        - documented liver transient elastography (eg, FibroScan) ≥20 kPa
        - AST/ALT >1.
4. Has a history confirming NASH cirrhosis, with at least one of the following:

    - There is a historical liver biopsy showing cirrhosis with steatohepatitis. There is no evidence for a competing etiology for the cirrhosis (if slides or blocks are not available, the biopsy report must clearly indicate cirrhosis with steatohepatitis).

    - There is a historical liver biopsy showing steatohepatitis (if slides or blocks are not available, the biopsy report must clearly indicate steatohepatitis), and there is evidence of cirrhosis from clinical or imaging data or a second liver biopsy showing cirrhosis without all features of NASH (as the histological NASH lesions may have burnt out). There is no evidence for a competing etiology. There is at least 1 co-existing or history of metabolic comorbidity at Screening: obesity (with either body mass index [BMI] ≥30 kg/m^2 or waist circumference ≥102 cm [40 in,

men] or ≥88 cm [35 in, women], or by ethnically appropriate cutpoints); hypertension (either on anti-hypertensive drug therapy for at least 1 year or systolic/diastolic BP >140/80 mm Hg); Type 2 diabetes (glycated hemoglobin [HbA1c] ≥6.5%, or on anti-diabetic medication for at least 1 year); or dyslipidemia (triglycerides ≥150 mg/dL or on drug therapy for hypertriglyceridemia for at least 6 months; high-density lipoprotein cholesterol ≤40 mg/dL [men] or ≤50 mg/dL [women]) to corroborate a diagnosis of NAFLD.

- There is a historical liver biopsy showing cirrhosis with steatosis but not steatohepatitis (if slides or blocks are not available, the biopsy report must clearly indicate cirrhosis with steatosis). There is no evidence for a competing etiology. There are at least 2 co-existing (or history of) metabolic comorbidities (with obesity or diabetes being one of them) to corroborate a diagnosis of NAFLD.

- There is a historical liver biopsy showing steatosis (if slides or blocks are not available, the biopsy report must clearly indicate steatosis) but now with cirrhosis either by physical examination, imaging, or biopsy. If there is a current biopsy, it does not show evidence of steatosis or steatohepatitis as histological lesions may have burned out. There is no evidence for a competing etiology. There are at least 2 co-existing (or history of) metabolic comorbidities (with obesity or diabetes being one of them) to corroborate a diagnosis of NAFLD.

- Patient with cirrhosis with current or previous imaging showing steatosis. There is no liver histology available. There is no evidence for a competing etiology. There are at least two co-existing or history of metabolic comorbidities with obesity or diabetes being one of them to corroborate a diagnosis of NAFLD.

- For patients not meeting the above mentioned criteria, a screening liver biopsy is necessary.

Note: All liver biopsy blocks and/or slides for eligibility assessments (including those from historical biopsies, where available) will be reviewed by the central study pathologist while the patient is in Screening. Results from the central study pathologist must be available before the patient is randomized.

5. Absence of HCC by valid imaging (eg, ultrasound, CT scan, or MRI) within 6 months prior to randomization. If no such imaging result is available, then ultrasound imaging should be performed as part of standard of care.

6. Patients with diabetes mellitus can be enrolled, if they are adequately controlled on a stable antidiabetic medication(s) for at least 3 months before Screening, and their screening HbA1c is ≤9.5%.

7. Patients on therapeutic doses of vitamin E or taking pioglitazone can be enrolled if they are on a stable regimen for at least 3 months before screening, and the regimen is expected to be held constant during the trial.

8. Patients on a statin can be enrolled if they are on a stable regimen for at least 3 months before Screening, and expected to be held stable during the trial.
9. Is not pregnant and must have a negative serum pregnancy test result prior to randomization.
10. Is of non-childbearing potential or if a fertile man or woman participating in heterosexual relations, agrees to use two acceptable means of contraception (ie, 2 effective methods of contraception, one of which must be a physical barrier method [eg, male or female condom, diaphragm] when combined with a highly effective method of contraception [ie, a method with a failure rate of <1% per year when used consistently and correctly]) throughout his/her participation in this study and for 90 days after discontinuation of study treatment.

    Highly effective forms of contraception include:

    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (such as oral, intravaginal, transdermal) methods
    - progestogen-only hormonal contraception associated with inhibition of ovulation (such as oral, injectable, implantable)
    - hormone-releasing intrauterine system (IUS)
    - intrauterine device (IUD)
    - bilateral tubal occlusion
    - a vasectomized partner, provided that partner is the sole sexual partner of the women of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success
    - sexual abstinence (ie, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods) are not acceptable methods of contraception. Surgically sterile males and females are not required to use contraception provided they have been considered surgically sterile for at least 6 months. Surgical sterility includes history of surgically successful vasectomy, hysterectomy, or bilateral salpingo-oophorectomy. Postmenopausal women who have been amenorrheic for at least 2 years at the time of Screening will be considered sterile.

11. If a lactating woman, agrees to discontinue nursing before the start of study treatment and refrain from nursing until 90 days after the last dose of study treatment.

12. If a man, agrees to refrain from sperm donation throughout the study period and for a period of 90 days following the last dose of investigational medicinal product (IMP). Female patients may not begin a cycle of ova donation or harvest throughout the study period and for a period of 90 days following the last dose of IMP.

4.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Presence of esophageal, gastroesophageal, or isolated gastric varices, based on an upper GI EGD exam conducted during Screening. Patients with portal hypertensive gastropathy (PHG) could be enrolled.

2. History of hepatic cirrhosis decompensation including any episode of variceal bleeding, ascites not controlled by medication, spontaneous bacterial peritonitis or overt hepatic encephalopathy (West Haven grade ≥2 as assessed by the principal investigator), OR develops signs of hepatic cirrhosis decompensation during Screening.

3. Known or suspected abuse of alcohol (>20 g/day for women or >30 g/day for men [on average per day]), as per medical history. Significant alcohol consumption is defined as more than 20 grams per day in females and more than 30 grams per day in males. On average, a standard drink in the US is considered to be 14 grams of alcohol, equivalent to 12 fluid ounces of regular beer (5% alcohol), 5 fluid ounces of table wine (12% alcohol), or 1.5 fluid ounces of 80 proof spirits (40% alcohol) (Appendix 9).

4. Alcohol dependence (ie, a score >8 on the Alcohol Use Disorders Identification Test [AUDIT]) (Appendix 6)

5. Narcotics or any other drug abuse or dependence in the last 2 years

6. Prior trans-jugular intrahepatic portal-systemic (TIPS) shunt procedure

7. Documented causes of liver disease other than NASH, including but not restricted to:
   - Viral hepatitis, unless eradicated at least 3 years prior to Screening
     - acute hepatitis A infection (presence of hepatitis A immunoglobulin M [IgM] at Screening)
     - positive hepatitis B surface antigen
     - positive hepatitis C virus (HCV) ribonucleic acid (to be performed prior to randomization in case of positive HCV antibody)
   - Documented drug-induced liver disease
   - Alcoholic liver disease
   - Autoimmune hepatitis
   - Wilson's disease
   - Hemochromatosis
   - Primary biliary cholangitis
   - Primary sclerosing cholangitis
   - Genetic hemochromatosis

- History or planned liver transplantation
- Alpha-1 antitrypsin deficiency

8. History of human immunodeficiency virus (HIV), or positive HIV test at Screening

9. Any of the following test or score:
   - serum ALT > 5 × upper limit of normal (ULN)*
   - serum AST > 5 × ULN*

     *Screening values will be obtained at SV1 and SV2 (which will be separated by 2 to 4 weeks). For the elevated transaminases that are above ULN, the following conditions will apply. A second screening value that is >50% higher than the first value should prompt re-evaluation of the severity of the underlying liver disease and eligibility for this trial. If a transaminase level at SV2 is >33% different from the level at SV1, then additional measurements should be performed at SV3. In such cases, the baseline transaminase levels will be established for patients using the mean value of 4 evaluations [ie, at SV1, SV2, SV3, and Baseline (ie, pre-dose during Visit 1)]. Transaminase level estimates are described in Section 4.4.4.1.
   - serum ALP > 2 × ULN
   - mean platelet count <50,000/mm^3
   - total bilirubin ≥2.0 mg/dL (patients with a documented history of Gilbert's syndrome can be enrolled if the direct bilirubin is within normal reference range)
   - MELD score >12 (patients on warfarin will be exempt from this criterion)
   - CTP Score ≥7

     Note: Following Phase 2b, patients with CTP scores ≥7 may be enrolled if recommended* by the DSMB and approved by the TSC, based on the planned IA. [*based on DSMB review of preliminary results from a separate hepatic impairment clinical trial (Study GT-032) which is assessing belapectin safety and PK in cirrhotic patients with CTP scores ≥7.
   - estimated glomerular filtration rate <45 mL/min*

     *Note: per Modification of Diet in Renal Disease algorithm (see Appendix 10)

10. Taking an angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, or β-1 selective adrenergic receptor inhibitor, unless on a stable regimen for at least 3 months prior to Screening and no changes in the regimen are anticipated during the study. Patients taking a non-selective beta blocker are not eligible to be enrolled (Investigators are encouraged to substitute another medication, if clinically warranted).

11. History of major surgery during Screening.

12. History of a solid organ transplant requiring immunosuppressive therapy.

13. History of bariatric surgery within 1 year of randomization, or plan to undergo bariatric surgery during the study.

14. Has positive screening test for illicit drugs of abuse at Screening. Positive marijuana/ cannabinoids (THC) usage is not an automatic exclusion, but rather should be based upon local requirements where applicable.
15. Has participated in an investigational new drug study within 30 days or 5 half-lives whichever is longer, prior to randomization.
16. Has a history of malignancy within 5 years of randomization, except for basal cell carcinoma, squamous cell carcinoma, and adequately treated in situ uterine cervical cancer.
17. Has clinically significant cardiovascular disease (eg, uncontrolled hypertension, myocardial infarction, unstable angina), New York Heart Association Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring intervention (eg, pacemaker/ablation) or Grade II or greater peripheral vascular disease.
18. Has a history of clinically significant hematologic, renal, hepatic, pulmonary, neurological, psychiatric, gastrointestinal, systemic inflammatory, metabolic or endocrine disorder or any other condition that, in the opinion of the Investigator, renders the patient a poor candidate for inclusion into the study.
19. Has known allergies to the IMP or any of its excipients.
20. Has previously received belapectin within 6 months of randomization.
21. Is an employee or family member of the Investigator or study center personnel.

4.3. Contraception

If a fertile man or woman participating in heterosexual relations, agrees to use two acceptable means of contraception (ie, 2 effective methods of contraception, one of which must be a physical barrier method [eg, male or female condom, diaphragm] when combined with a highly effective method of contraception [ie, a method with a failure rate of <1% per year when used consistently and correctly]) throughout his/her participation in this study and for 90 days after discontinuation of study treatment.

Highly effective forms of contraception include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (such as oral, intravaginal, transdermal) methods
- progestogen-only hormonal contraception associated with inhibition of ovulation (such as oral, injectable, implantable)
- hormone-releasing IUS
- IUD

- bilateral tubal occlusion

- a vasectomized partner, provided that partner is the sole sexual partner of the women of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success

- sexual abstinence (ie, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods) are not acceptable methods of contraception.

Surgically sterile males and females are not required to use contraception provided they have been considered surgically sterile for at least 6 months. Surgical sterility includes history of surgically successful vasectomy, hysterectomy, or bilateral salpingo-oophorectomy. Postmenopausal women who have been amenorrheic for at least 2 years at the time of Screening will be considered sterile.

If a lactating woman, agrees to discontinue nursing before the start of study treatment and refrain from nursing until 90 days after the last dose of study treatment. If a man, agrees to refrain from sperm donation throughout the study period and for a period of 90 days following the last dose of IMP. Female patients may not begin a cycle of ova donation or harvest throughout the study period and for a period of 90 days following the last dose of IMP.

4.4. Discontinuation Criteria

4.4.1. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. All the screen failure information and associated testing including central laboratory data will be captured in the database.

4.4.2. Rescreening

Patients who fail to meet eligibility criteria during the screening period due to an abnormal central laboratory result may undergo retesting of the abnormal central laboratory parameter during the screening window, at the discretion of the Investigator.

Re-screening is allowed in a screen failed patient if there is a change in the situation of the patient which allows him/her to fulfill inclusion/exclusion criteria.

In case of re-screening the patient will need to sign a new informed consent and will be entered as a new patient, with a new patient number.

Re-screening is only allowed after Medical Monitor's approval.

All the information will be captured in the database.

4.4.3. Discontinuation of Study Treatment

In some instances, it may be necessary for a patient to permanently discontinue study drug. The patient may be discontinued from study drug at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons.

The reason for permanent discontinuation of study drug should be documented in the electronic Case Report Form (eCRF) and the Medical Monitor informed. A discussion between the Principal Investigator, the Medical Monitor, and the Sponsor should take place before a decision to permanently discontinue the study drug is made. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF. Some possible reasons that might lead to permanent early study drug discontinuation include:

- The patient develops large varices, varices with red wales, variceal hemorrhage or portal gastropathy hemorrhage, confirmed by endoscopy (please refer to the separate EGD Charter) or any other complications of cirrhosis which the patient develops (eg, ascites, hepatic encephalopathy) which cannot be medically controlled
- Adverse events or laboratory safety assessments that reveal clinically significant hematological or biochemical changes from the baseline values that justifies withdrawal of study drug.
- The patient requests to stop study drug permanently.
- Female patients who are pregnant or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug

In all cases, patients will be censored at the time of study drug discontinuation. Except for pregnant women, patients will continue the study visits and safety follow-up. Any clinical outcome, AE or SAE will be captured in eCRF. Invasive study assessments (eg, EGD) are not mandatory and will be performed based on the Investigator's judgement. Patients will receive treatment following the local guidance for the management of these complications. If patients cannot continue with study visits, efforts will be made to capture clinical outcomes through medical records or phone calls.

Patients permanently discontinued from study drug in Phase 2b or Phase 3 will attend an Early Termination Visit within 14 to 28 days after the last infusion of study drug and an EOS Visit 14 days after the Early Termination Visit. Patients who discontinue in Phase 2b (prior to Week 78) will not be eligible to participate in Phase 3.

All the information will be captured in the database.

4.4.4. Withdrawal from the Study

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study center. Every effort should be made to retain the patient in the study. The reasons for patients not completing the study will be recorded. A patient may be withdrawn from the study for any of the following reasons:

- Significant noncompliance with the protocol. Principal Investigator should discuss with Medical Monitor prior to permanently discontinuing any patient from the trial
- If patients develop an AE of NCI-CTCAE Grade 4 that is related or possibly related to IMP they will be discontinued from the trial (NCI-CTCAE v5.0, publication date: November 27, 2017). Patients who develop an AE of NCI-CTCAE Grade 3 that is related or possibly related to IMP will be considered for drug discontinuation.
- Symptoms or an intercurrent illness not consistent with the protocol requirements for study participation or that justifies withdrawal.
- Lost to follow-up (see Section 4.4.5)
- Death
- Undergoing liver transplant
- The patient develops ascites that cannot be medically controlled (ie, no surgical intervention required) or overt hepatic encephalopathy that cannot be controlled by medical management.
- Patients who develop spontaneous bacterial peritonitis that cannot be controlled by medical management
- Patients who develop fever, rash, and/or jaundice will be considered for withdrawal.
- Inability to maintain IV access for infusion of IMP, either through intermittent or in dwelling access.
- The patient withdraws consent or the Investigator or Sponsor decides to discontinue the patient's participation in the study.

The Investigator should also withdraw patients if the Sponsor terminates the study.

4.4.4.1. Potential Drug-Induced Liver Injury

Baseline transaminase levels will be established for patients using the mean value of 3 evaluations: SV1 and SV2 (which will be separated by 2 to 4 weeks) and Infusion Visit 1 (pre-infusion). For elevated baseline transaminases (above ULN), the following conditions will apply. A second screening value >50% higher than the first one should prompt re-evaluation of the severity of the underlying liver disease and eligibility for the trial. If the transaminase level at SV2 is >33% different from the level at SV1, then additional measurements should be performed at SV3. In such cases, the baseline transaminase levels will be established for patients using the mean value of 4 evaluations (ie, at SV1, SV2, SV3 and Infusion Visit 1 pre-dose).

Note: For patients that continue into Phase 3, the established baseline values for Phase 2b liver function tests and other routine blood test values will serve as baseline for both the Phase 2b and Phase 3 periods.

Total bilirubin, direct bilirubin, and INR will be tested at SV1 to establish the eligibility and at SV2 to determine if the patient's underlying liver disease is worsening prior to initiation of study drug. Baseline values for total bilirubin, direct bilirubin, and INR will be taken pre-dose at Infusion Visit 1 in Phase 2b and Phase 3 for patients entering the study de novo in Phase 3.

For evaluation of potential DILI, guidelines recommend a different approach in patients with normal baseline ALT and patients with elevated baseline ALT values. Normal baseline ALT is defined as the mean ALT values from SV1, SV2, SV3 (if applicable) and pre-dose Infusion Visit 1 < 1.5 × ULN; elevated baseline ALT is defined as the mean values of ALT ≥ 1.5 × ULN.

Emergence of ALP ≥ 2 × ULN is not typical of NASH and should prompt an evaluation for an alternative etiology including DILI.

For patients with normal baseline ALT:

- ALT 3 to 5 × ULN: perform close monitoring

  If during retest:

  - ALT remains 3 to 5 × ULN: continue study treatment with monitoring once a week
  - ALT increases to > 5 × ULN: discontinue study treatment
- ALT > 5 × ULN: perform close monitoring
  - If during monitoring ALT increases: discontinue study treatment
  - If during monitoring, ALT remains >5 × ULN for 2 weeks: discontinue study treatment

Discontinue study treatment immediately and initiate close monitoring in the following cases:

- ALT > 8 × ULN
- ALT > 5 × ULN for more than 2 weeks
- ALT > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5
- ALT > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Isolated jaundice or decompensation events.

For patients with elevated baseline ALT:

- ALT > 3 × baseline but < 10 × ULN: perform close monitoring
  - If during monitoring, ALT remains > 3 × baseline but < 10 × ULN: continue study treatment with monitoring once a week
  - If during monitoring, ALT increases to > 5 × baseline or > 10 × ULN: discontinue study treatment

- ALT > 2 × baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%): perform close monitoring
    - If during monitoring, ALT increases or symptoms have not resolved: discontinue study treatment

Discontinue study treatment immediately and initiate close monitoring in the following cases:

- ALT > 5 × baseline or > 10 × ULN (whichever occurs first)
- ALT > 2 × baseline or > 5 × ULN (whichever occurs first) and total bilirubin > 2 × ULN or INR > 1.5
- ALT > 3 × baseline or > 5 × ULN (whichever occurs first) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Isolated jaundice or decompensation events.

Close monitoring includes repeat ALT, AST, ALP, total bilirubin, in 48 to 72 hours; follow-up for symptoms; and initiation of evaluation for competing etiologies of abnormal liver tests.

If a patient meets discontinuation criterion, continue monitoring until the laboratory elevations/symptoms have resolved or stabilized, or until a determination of a cause unrelated to the study drug is made.

All potential DILI events will be adjudicated by a blinded Clinical Evaluation Committee (see Section 7.5).

4.4.4.2. Electrocardiogram (ECG) Changes

In patients with liver cirrhosis, prolongation of the QT interval is common, with a prevalence of 60% to 80% cited in the literature in patients with advanced stages of cirrhosis.[37-39]

If a clinically significant ECG finding is identified (including, but not limited to changes from baseline in QT interval corrected using Bazett's formula or Fridericia's formula) after enrollment, the Investigator or qualified designee will determine whether the patient can continue in the study and if any change in patient management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Note: For patients that continue into Phase 3, the established ECG values for Phase 2b will serve as baseline for both the Phase 2b and Phase 3 periods.

A patient who meets the bulleted criterion based on the average of triplicate ECG readings will be assessed by a cardiologist for study continuation.

- Absolute QTc interval prolongation: >480 msec, OR
- Change from baseline in QTc interval >60 msec.

4.4.4.3. Major Adverse Cardiovascular Events (MACE) Definition

Major adverse cardiovascular events (MACE; defined for this study as myocardial infarction, hospitalization for unstable angina, stroke/transient ischemic attack, and heart failure) will be adjudicated by the Clinical Events Committee (CEC; see Section 7.5).

4.4.4.4. Treatment Interruption

Treatment interruptions should be avoided. All the missed doses will be recorded in the study records along with the reason for the missed dose(s). A drug interruption occurring at any time outside the prespecified treatment window during any period will be considered a protocol deviation.

4.4.5. Lost to Follow-up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.

- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (this should include 3 telephone calls, emails, or a combination of both and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up and the last date of contact will be recorded.

4.4.6. Replacement Procedures

No patients will be replaced.

4.5. Study Termination

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. Reasons for study termination may include, but are not limited to:

- AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of drug development
- DSMB recommendations
- Change in the opinion of the Institutional Review Board (IRB)/Ethics Committee (EC) or regulatory authority decision

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a reasonable period of time. As directed by the Sponsor, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

In all cases, ethics committee (IRB/EC) and Health Authorities should be informed. If the Investigator decides to prematurely discontinue the study, all test articles, eCRFs, and related study materials must be returned to the Sponsor.

5. STUDY TREATMENTS

5.1. Treatments Administered

During Stage 1 (Phase 2b), patients will be randomly assigned to receive 2 mg/kg LBM, or 4 mg/kg LBM, or placebo in a 1:1:1 ratio. An interactive web response system (IWRS) will be used to administer the randomization schedule using SAS® software version 9.4 (SAS Institute Inc., Cary, North Carolina), which will link sequential patient randomization numbers to treatment codes. Randomized patients will be stratified by type 2 diabetes status.

For Stage 2 (Phase 3), the optimal dose level of belapectin (2 or 4 mg/kg LBM) will be selected by the DSMB, and approved by the TSC, based on the IA after Phase 2b. Patients completing Phase 2b will continue into Phase 3 for 78 weeks (18 months) at the belapectin dose chosen at the IA or will continue with placebo treatment. For patients who start Phase 3 prior to the IA, they will continue on their current treatment until IA and may be switched to a modified dose based on the results of the IA. Patients newly enrolled directly into Phase 3 will be randomized in a 2:1 ratio to either the optimal dose of belapectin or placebo.

Belapectin for injection is supplied in a sterile aqueous solution of phosphate-buffered saline at a concentration of 27 mg/mL belapectin and should be diluted to the target dose in 100 mL of normal saline and administered IV over a period of 60 minutes (± 12 minutes). The product is expected to be stable at pH 4.0 to 7.5.

Intravenous access will be achieved by intermittent placement of an IV catheter at the time of the IMP infusion. In cases where intermittent IV access cannot be maintained after randomization of a patient, an indwelling IV access catheter (eg, port-a-cath) can be utilized to complete the IV infusions and be maintained for access for the duration of the study, at the discretion of the Investigator and agreement/training of the patient. If the Investigator does not feel that an indwelling catheter is feasible or appropriate for the patient, or if the patient refuses this intervention, the patient will be withdrawn from the trial.

Belapectin will be supplied to the study sites with the following composition:

Ingredient	Quantity
Belapectin	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Instructions on dosing preparation are provided in the Pharmacy Manual.

Once the infusion solutions are prepared, they may be held at room temperature (20ºC to 25ºC [68ºF to 77ºF]) for up to 4 hours or stored under refrigerated conditions (2ºC to 8ºC [36ºF to 46ºF]) for up to 24 hours. Infusions should be administered via IV over a period of 60 minutes (±12 minutes). Frequency of administration should be once every 2 weeks (Appendix 5).

Following completion of the infusion, the patient should be observed for at least 30 minutes or the relevant time as mandated by the protocol of the site infusion center.

5.2. Preparation, Storage, Handling, and Accountability

Belapectin (galactoarabino-rhamnogalacturonate) is a soluble polysaccharide composed of an alternating [redacted].

Belapectin for injection is a clear, light yellow-tan solution and is supplied in 10-mL sterile vials at a concentration of 27 mg/mL of belapectin in phosphate-buffered saline.

Detailed instructions for the preparation and administration of the belapectin by slow IV infusion over a period of 60 minutes (± 12 minutes) are provided in the Pharmacy Manual.

Lean body mass will be used for dose calculations because it is anticipated that many patients will be obese and belapectin is distributed primarily in the blood compartment. Lean body mass will be estimated by IWRS from height and weight measurements using the formulas that have been well-validated in obese individuals[33]:

Males: LBM = [9270 × total body weight (TBW)] / [6680 + (216 × BMI)]

Females: LBM = [9270 × TBW] / [8780 + (244 × BMI)]

Total body weight is in kilograms and BMI is in mass (weight in kilograms) / (height in meters^2). BMI will be calculated by IWRS.

Tables of LBM values for a range of heights and weights will be provided to the pharmacies participating in the study as a check for the calculations. LBM will be automatically calculated by IWRS and automatically calculated and displayed on the CRF page.

The study pharmacist and/or a study nurse (or equivalent individuals approved by the Investigator) at each study center will be unblinded in the preparation of study drug. To maintain the blind, the unblinded pharmacist and/or unblinded nurse will have limited contact with blinded study personnel to prevent disclosure of the blinded treatments. Infusion solutions will be prepared as specified in the Pharmacy Manual. Once prepared by the unblinded pharmacist and/or unblinded nurse, the placebo and drug solutions in the IV infusion set up will be indistinguishable. Thus, the study patients, Investigators, and medical personnel administering the infusion will be blinded throughout the study as to whether the patient is receiving active drug or placebo.

The following drug supplies will be used in the study:

- Belapectin, supplied as 10-mL sterile vials
- Placebo ([redacted] supplied as 10-mL sterile vials

Belapectin for injection and placebo (in 10-mL vials to be used for the study are manufactured for Galectin Therapeutics by .

The belapectin for injection vials and placebo vials are to be stored under refrigerated conditions at 2°C to 8°C (36°F to 46°F) until preparation of the drug infusion solution. To prepare the final infusion solution for administration, the belapectin will be diluted in sterile normal saline as required to achieve the target dose. Instructions on dosing preparation are provided in the Pharmacy Manual.

The Investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, IMP will be reconciled and retained or destroyed according to applicable regulations.

5.3. Method of Treatment Assignment

All patients will be centrally randomized using an IWRS. Before the study is initiated, the telephone number and call-in directions for the IWRS and/or the log in information and directions for the IWRS will be provided to each site.

Patients who roll-over from Phase 2b to Phase 3 will continue for the 78 weeks (18 months) during Phase 3 (Stage 2) and will continue belapectin treatment (at the same or a modified dose) during Phase 3 or continue treatment with placebo. These patients will not be re-randomized. For patients who start Phase 3 prior to the IA, they will continue on their current treatment until IA and may be switched to a modified dose based on the results of the IA.

Patients newly enrolled in Phase 3 will be randomized in a 2:1 ratio to either the selected dose of belapectin or placebo.

Study treatment will be dispensed at the study visits summarized in the Schedule of Assessments (Appendix 5).

5.3.1. Dose Modification

No dose modification for an individual will occur unless BMI increases ≥10% above baseline.

5.3.2. Overdose

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the IB. Any overdose, with or without associated AEs, must be promptly reported in the same manner as SAEs (Section 7.2.3.10). Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported in relevant AE/SAE sections in the eCRF.

There are no known or anticipated adverse effects of belapectin overdose. Belapectin has been safely administered to cirrhotic NASH patients, in a Phase 2 trial, at doses up to 8 mg/kg LBM IV without notable AEs. The patient should be observed, but there are no specific therapies to be instituted. Any overdosing will be recorded on the appropriate pages in the eCRF.

5.3.3. Medication Errors

A medication error is any unintentional error in prescribing, dispensing, or administration of the IMP. The IMP will be prepared and administered at the study center by trained personnel, thereby reducing the risk of medication errors. Optional home administration by trained personnel will be allowed, if needed in certain visits, only with prior agreement with Sponsor.

Acceptable treatment windows for infusions will be ± 3 days of the planned visit. Infusions given outside of accepted windows will be considered "out-of-window" doses. If a dose is out of window, the patient should be brought back into compliance with his or her visit dosing schedule. The patient should not dose within 7 days of the previous or next dose unless the Medical Monitor is consulted and agrees.

Medication errors and any AEs resulting from medication errors will be recorded as AEs in the eCRF.

Belapectin does not have known effects that may be addictive and there are no other known reasons for misuse.

5.4. Blinding

This is a double-blind study.

Unblinded site staff should not be involved in the direct administration of the study drug infusion to the patient but instead a blinded nurse should be responsible for the infusion. To maintain the blind, the unblinded pharmacist and/or unblinded nurse will have limited contact with blinded study personnel to prevent disclosure of the blinded treatments. Infusion solutions will be prepared as specified in the Pharmacy Manual. Once prepared by the unblinded pharmacist and/or unblinded nurse, the placebo and drug solutions in the IV infusion set up will be indistinguishable. Thus, the study patients, Investigators, and medical personnel will be blinded throughout the study as to whether the patient is receiving active drug or placebo.

Infusion of the IMP is not commonly known to cause local reaction in animal studies or in humans participating in the Phase 1 or 2 studies and should not affect blinding.

A patient's treatment assignment will not be broken until the end of the study unless medical treatment of the patient depends on knowing the study treatment the patient received. In the event that the blind needs to be broken because of a medical emergency, the Investigator may unblind an individual patient's treatment allocation. Emergency unblinding should also be available to a third party physician/medical professional who is not participating in the study (eg, staff in hospital emergency room). As soon as possible, the Investigator should first contact the Medical Monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that patient. However, this may not be mandatory and should not cause

any delay in unblinding in case of emergencies. The treatment assignment will be unblinded by the Investigator through IWRS. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented. Galectin must be notified within 24 hours after breaking the blind.

5.5. Treatment Compliance

Patient compliance will be determined by infusion records.

Acceptable windows for IMP dosing are ± 3 days of the planned visit. Infusions given outside of accepted windows will be considered "out-of-window" doses. If a dose is out of window, the patient should be brought back into compliance with his or her visit dosing schedule. The patient should not dose within 7 days of the previous or next dose unless the Medical Monitor is consulted and agrees.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

Use of all concomitant medications will be recorded in the patient's eCRF. The minimum requirement is that drug name, reason for use, dose, and dates of administration will be recorded. Any changes in the concomitant medications will also be recorded in the patient's eCRF.

All prior treatments for liver cirrhosis and NASH (up to 5 years prior to screening) will be recorded in the eCRF. All other prior and concomitant medications taken from 30 days prior to screening and throughout the entire duration of the patient's participation in the study will be documented in the eCRF.

Concomitant medications are defined as medications taken any time after the start of exposure to IMP. Prior medications are defined as non-study medications discontinued prior to start of exposure to IMP. All the prior medications will be recorded on an appropriate eCRF page.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. If prohibited medications are needed for the welfare of the patient, the continuation of the patient in the study should be discussed with the Medical Monitor. It is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.2. Prohibited and Permitted Medications or Therapies

Patients on therapeutic doses of vitamin E or taking pioglitazone can be enrolled if they are on a stable regimen for at least 3 months before screening and the regimen is expected to be held constant during the trial.

Patients with diabetes mellitus can be enrolled if they are adequately controlled on a stable antidiabetic medication(s) for at least 3 months before Screening.

Patients taking a statin, angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, or β-1 selective adrenergic receptor inhibitor should be excluded from the study unless on a

stable regimen for at least 3 months prior to screening and are expected to maintain their regimen during the trial.

Patients taking non-selective beta blockers will not be allowed to enter this study. Ocaliva (obeticholic acid) is not allowed during the study.

Cyanoacrylate injections are not recommended for primary prophylaxis against variceal hemorrhage for gastroesophageal varices and are not encouraged. Endoscopic sclerotherapy, oral nitrates and TIPS should not be allowed for primary prophylaxis of variceal hemorrhage in patients who develop varices after baseline. Any of the above mentioned procedures and drugs or drugs which can cause liver damage (as per the prescribing information) should only be used after discussion with the Investigator, Medical Monitor, and the Sponsor.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments (Appendix 5). As protocol waivers or exemptions are not allowed, with the exception of immediate safety concerns, any major deviations should be discussed with the Medical Monitor and the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue the study drug. Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screen failure (Section 4.4.1), as applicable.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

7.1. Study Visit Schedule

The details of the assessments to be performed during each visit are presented in Appendix 5.

7.1.1. Identification of Patients and Screening

Identification of Patients for Phase 2b and of New Patients Entering Phase 3

Prior to signing the ICF, potential patients will be assessed by the Investigators for the likelihood of having NASH cirrhosis (based on documented medical history and historical liver biopsy, if available), and without varices (based on historic EGD if available), and then advance to Screening as described in Section 3.1.

Screening for Phase 2b or Phase 3

Following informed consent, assessments for eligibility (by inclusion and exclusion criteria) will be done within 10 weeks (2.5 months) before randomization, as follows:

- Medical, surgical and medication history, vital signs (heart and respiratory rate, BP, and body temperature), complete physical examination, including height, weight, BMI, ECG, and central clinical laboratory evaluations (hematology, chemistry, coagulation profile, urinalysis, specialized tests for specific liver diseases, serology), chest radiographs (chest radiographs will not be performed for patients enrolled at sites in Germany due to local regulations), drugs of abuse screening test, alcohol timeline followback (TLFB), AUDIT questionnaire, MELD score, CTP score, and pregnancy test [both urine and serum, for women of childbearing potential] [Appendix 3]).

- Clinical signs of portal hypertension, with either one of the following: (a) platelet count <150,000/mm^3 (from central laboratory or historical record, such as detailed chart notes providing platelet numbers or copies of laboratory reports showing platelet count[s] below 150,000/mm^3) or (b) documented HVPG measurement >6 mmHg

OR

(c) at least two of the following: spleen size ≥14 cm by imaging (ultrasound, MRI, or CT scan), evidence of abdominal collateral circulation (by ultrasound, MRI, or CT scan or caput medusae seen upon physical examination), or documented liver transient elastography (eg, FibroScan) ≥20 kPa or AST/ALT >1.

- EGD with video recording documentation to confirm the presence or absence of esophageal varices.
- Liver and abdomen ultrasound exam to screen for HCC and for ascites.
- Liver biopsy, while not required, can be used to confirm diagnosis of NASH cirrhosis by the central pathologist, if necessary. (A historic liver biopsy is acceptable if the biopsy blocks and/or slides are available for central review.) Results from the central study pathologist must be available before the patient is randomized.

Note: It is not required for all of the assessments above to be performed on the same day. All appropriate steps should be taken to ensure study-related assessments are completed and results available within the 10-week screening period, with the exception of delays in laboratory results (including biopsy) and EGD reporting which were not due to site delays in performing these examinations.

7.1.2. Randomization and Treatment

Randomization

Randomized patients will be stratified by Type 2 diabetes status.

For Stage 1 (Phase 2b) of this study, randomization will occur on Week 0, Day 0 (infusion 1). Prior to Infusion Visit 1, eligible patients will be randomly assigned in 1:1:1 ratio to receive 1 of 3 treatments: belapectin at a dose of 2 mg/kg LBM or 4 mg/kg LBM, or placebo.

Patients who complete Phase 2b (Stage 1) will continue into Phase 3 (Stage 2). Those patients who received belapectin during Phase 2b will continue belapectin treatment (at the same or a modified dose) during Phase 3. For patients who start Phase 3 prior to the IA, they will continue on their current treatment until IA and may be switched to a modified dose based on the results of the IA. Those patients who received placebo during Phase 2b will continue placebo treatment during Phase 3.

Patients newly enrolled in Phase 3 will be randomized in a 2:1 ratio to either the selected optimal dose of belapectin or placebo.

Treatment Phase

The following efficacy assessments will be carried out during the treatment phase of the Stage 1 (Phase 2b) and Stage 2 (Phase 3) parts of the study:

- EGD with video documentation, to assess varices at the end of Phase 2b, and at the end of Phase 3, or upon early discontinuation at any visit. An independent endoscopy review expert panel will review all EGD records (including the baseline EGD), and adjudicate all assessments.

- Transient elastography (eg, FibroScan) to assess liver stiffness, approximately every 6 months

- Blood samples for liver enzymes (eg, ALT, AST, ALP, GGT) and liver function tests (eg, bilirubin, albumin, INR) and platelet counts will also be drawn periodically, together with routine central clinical laboratory tests for safety monitoring during scheduled study center visits, as indicated in the protocol Schedule of Assessments.

- At the start and end of Phase 2b and the start (for newly-enrolled patients) and end of Phase 3, and at time points indicated in the schedule of assessments, a blood sample will be stored (-80°C) for other possible poststudy biomarker tests and gene expression analysis.

Final Visit and Early Termination Visit/ End of Treatment Visit

Patients who discontinue Phase 2b early (prior to Week 78) will have an Early Termination Visit (14 to 28 days after their last dose), and will not be eligible to participate in Phase 3.

Patients completing Phase 3 will have an End of Treatment Visit 14 to 28 days after their last dose.

All patients will have a final visit (EOS Visit) 14 days after the Early Termination/End of Treatment Visit.

7.2. Study Assessments

7.2.1. Efficacy Assessments

7.2.1.1. FibroScan

FibroScan is a US Food and Drug Administration-approved, non-invasive diagnostic instrument that uses an electromechanical vibrator and pulse-echo ultrasound to evaluate the elastic shear wave in liver tissue which is a measure of liver stiffness. The stiffness of the liver is recorded as the pressure measurement in kPa units. The stiffness of the liver correlates with the degree of liver fibrosis as assessed by liver biopsy, including in patients with NASH.[30] One advantage of this method is that the volume of liver tissue assessed is approximately 100 times greater than the volume assessed by liver biopsy. As such, FibroScan represents a promising non-invasive, outpatient method for measuring changes in liver fibrosis over time.

Trained personnel will perform all VCTE examinations with the FibroScan instrument, using a standardized procedure. Patients will be placed in supine position with the right arm in maximal abduction and measurements will be taken over the right hepatic lobe through an intercostal space. If possible, all studies will be started using the M probe with transition to the XL probe

(for obese individuals) if prompted by the device's automatic probe selection tool. If there is no available device with the automated selected probe, the selection will follow the indications in study guidelines provided in the Study Manual and as per the manufacturer's instructions. Only cases with ≥10 valid acquisitions will be used. Both median and interquartile range value will be captured. To help ensure consistency, when possible, the same certified operator will repeat the VCTE at subsequent timepoints specified in the protocol schedule of assessments (Appendix 5).

Food intake (within 60 minutes) has been found to be associated with falsely high LSM values. Patients will be required to have fasted at least 3 hours with no alcohol intake and no physical activity during the prior 3 hours.

An effort will be made to include study sites at which FibroScan is available, either located at the site or in the vicinity of the study site. For these sites, FibroScan should be obtained at all of the appropriate times indicated in the protocol. At the discretion of the Sponsor, sites may be included that are unable to perform FibroScan.

7.2.1.2. Child-Turcotte-Pugh Score

The CTP Score provides an assessment of the prognosis of chronic liver disease. In this classification system, various central laboratory and clinical parameters are scored as shown in Table 1.

Table 1 Child-Turcotte-Pugh Scoring System

Categories	Scoring System
Bilirubin	+1: <2 mg/dL +2: 2-3 mg/dL +3: >3 mg/dL
Albumin	+1: >3.5 g/dL +2: 2.8-3.5 g/dL +3: <2.8 g/dL
International normalized ratio	+1: <1.7 +2: 1.7-2.2 +3: >2.2
Ascites	+1: No ascites +2: Ascites, medically controlled +3: Ascites, poorly controlled
Encephalopathy	+1: No encephalopathy +2: Encephalopathy, medically controlled +3: Encephalopathy, poorly controlled

The total score determines the classification as shown in Table 2.

Table 2 Child-Turcotte-Pugh Classification

Points	Class	One-year Survival	Two-year Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Initial study protocol criteria allow inclusion into Phase 2b of only patients with Class A, wellcompensated cirrhosis. However, after the IA and upon recommendation of the DSMB, patients with higher CTP scores (≥7) might become eligible to participate in Phase 3.

7.2.1.3. Model for End-Stage Liver Disease Score

The MELD Score assesses the severity of chronic liver disease and is used for prioritizing allocation of liver transplants. The MELD score will be calculated from central laboratory tests (albumin, creatinine, bilirubin, and INR).

MELD Score = (0.957 × ln (serum creatinine) + 0.378 × ln (serum bilirubin) + 1.120 × ln(INR) + 0.643) × 10 (if hemodialysis, value for creatinine is automatically set to 4.0). The unit used for creatinine and bilirubin levels is µmol/L.

Note: If any score is less than 1, then MELD assumes the score is equal to 1.

Only patients with MELD score ≤12 are eligible (except patients on warfarin). Any patient with a MELD score ≥15 on two consecutive occasions will be adjudicated by the CEC (see Section 7.5).

7.2.1.4. Esophagogastroduodenoscopy Evaluation

Patients will undergo an EGD with video documentation during Screening to verify the inclusion criteria. Subsequently, patients will undergo EGD with video images of the esophagus and stomach at the end of Phase 2b (Week 78), and at the end of Phase 3 (Week 78), or upon early discontinuation at any visit. Each EGD will be done within 14 days of the scheduled visit as per Appendix 5.

Although several classification systems have been described, the classification of esophageal varices that is most comprehensively followed and endorsed is the Baveno consensus classification,[14] which is endorsed by the American Association for Study of Liver Diseases, the European Association for Study of the Liver and the Asian-Pacific Association for Study of the Liver societies. The Baveno consensus classifies varices (i) into small and large and (ii) the presence or absence of red color signs.

The classification of esophageal varices, gastroesophageal varices, and isolated gastric varices and other EGD assessments such as PHG are described in the EGD Charter.

A trained endoscopist should perform the endoscopy with a video recording. For each patient, EGD with video recording documentation should be performed by the same endoscopist at all visits, whenever possible. All results will be centrally read and adjudicated. Please refer to the EGD Charter for further detailed instructions and information.

Patients with any gastrointestinal varices detected during baseline screening, regardless of size or location, will be excluded from study participation. Patients without varices may advance to other study screening evaluations, and potential randomization.

7.2.1.5. Chronic Liver Disease Questionnaire

The CLDQ is a patient-reported outcome instrument used to measure HRQOL in patients with liver disease and has demonstrated good reliability and validity in patients with chronic liver disease.[31] The CLDQ includes 29 questions with 6 domains: abdominal symptoms, systemic symptoms, fatigue, activity, emotional function, and worry. The CLDQ will be given to the patient at the beginning of the visit (Appendix 5), and will be considered source documentation. The CLDQ is provided in Appendix 7 .

7.2.1.6. Assessment of Cirrhosis Complications

The following liver cirrhosis complications will be assessed during the study:

- Development of esophageal varices
- Progression of varices to become large varices or red wales
- Development of varices (esophageal or gastric) requiring treatment
- Development of variceal bleed (esophageal or gastric) requiring hospitalization
- Esophageal variceal hemorrhage or gastropathy hemorrhage, confirmed by endoscopy
- Clinically significant ascites requiring hospitalization
- Spontaneous bacterial peritonitis
- Overt hepatic encephalopathy (defined as West Haven Score ≥2 and requiring hospitalization)
- Hepatocellular carcinoma
- End-stage liver disease
- Liver transplant
- Change in MELD score to ≥15 on 2 consecutive occasions
- Change in CTP score from baseline, with increase of ≥2 points of two consecutive determinations
- Liver-related death
- All-cause mortality.

All cirrhosis-related complications will be adjudicated by the CEC (Section 7.5).

7.2.2. Biomarkers

Serum samples for an Enhanced Liver Fibrosis (ELF) test will be collected at the timepoints indicated in Appendix 5. [redacted]

Serum/plasma will be collected at the timepoints indicated in Appendix 5 and stored at -80°C for potential future assays of biomarkers and gene expression assays.

7.2.2.1. Plasma and Serum Samples

Samples will be stored at -20ºC or below; samples collected for long-term storage will be stored at -80ºC. A detailed procedure for sample collection and processing is presented in the Laboratory Manual.

7.2.3. Safety and Tolerability Assessments

7.2.3.1. Medical History and Demographics

Demographic characteristics (age, gender, race, ethnicity) will be recorded at Screening. A complete medical and surgical history and medication history will be recorded during Screening.

7.2.3.2. Vital Signs Measurements

Blood pressure (mm Hg) and pulse rate (beats per minute) will be measured at each visit according to the "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals" published in an American Heart Association scientific statement.[30,23]

Important points for clinical BP measurement are as follows:

- The patient should be seated comfortably with the back supported and the upper arm bare without constrictive clothing. The legs should not be crossed.
- The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference.
- When using a mercury sphygmomanometer, the mercury should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure, respectively. The column should be read to the nearest 2 mm Hg.
- Neither the patient nor the observer should talk during the measurement. Systolic BP and diastolic BP will be measured after 5 minutes rest in the seating position with a standard mercury sphygmomanometer or a validated sphygmomanometer. Where possible, the validated manometer should be the same for a given patient throughout the visits.

Vital signs will be measured at the timepoints indicated in Appendix 5.

7.2.3.3. Physical Examination

A complete physical examination including height (cm) and weight (kg), will be performed at Screening with particular attention to examination for signs of liver disease/cirrhosis (Appendix 5).

A limited physical examination will include weight and examination of the heart, lung, and abdomen. A limited physical examination will be carried out during the treatment phase (Appendix 5).

7.2.3.4. Electrocardiogram

A standard 12-lead ECG will be performed during Screening and the treatment phase (Appendix 5). All the ECGs will be locally read.

If there are clinically significant findings or concerns by the Investigator, a triplicate ECG should be performed and assessed for clinical significance by a local cardiologist, as stated in Section 4.4.4.2.

Twelve-lead ECG will be systematically digitally recorded after the patient has been in the supine position for at least 10 minutes. The electrodes will be positioned in the same location on the patient for each ECG recording. Electrocardiograms will be recorded before blood sampling.

7.2.3.5. Chest Radiographs

Chest radiographs (posterial-anterior and lateral views) will be performed at Screening (Appendix 5). Chest radiographs will not be performed for patients enrolled at sites in Germany due to local regulations.

7.2.3.6. Abdominal Imaging

Abdominal imaging for spleen size and/or the documentation of abdominal collateral circulation can be performed by ultrasound, MRI, or CT scan. Spleen size can be measured at any time point within the screening period, but prior to the liver biopsy (if the biopsy is needed) (Appendix 5).

7.2.3.7. Liver Ultrasound

Liver ultrasound will be carried out to assess for HCC and ascites every 6 months, per standard of care, as specified in the Schedule of assessments (Appendix 5).

7.2.3.8. Adverse Events

Adverse event definitions and assignment of severity and causality are detailed in Section 7.3.

Adverse events will be elicited from the patient (or, when appropriate, from a caregiver, surrogate, or the patient's legally authorized representative) by the study site staff using a non-leading question such as "How are you feeling today?" or "Have you had any health

concerns since your last visit?" Adverse events will be recorded after obtaining informed consent and through the end of the study for each patient.

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, irrespective of its relationship to the study treatment or the study, or that caused the patient to discontinue the study drug (see Section 4.4.3).

7.2.3.9. Suspected Liver-Related Clinical Outcome Events

Specified liver-related clinical outcome events may, by definition, qualify as SAEs (Section 7.3). However, for this study, given that the liver-related clinical outcome events could also meet the criteria of a suspected unexpected serious adverse reaction (SUSAR), which would necessitate unblinding for expedited reporting, the Sponsor will not expeditiously report suspected liver-related clinical outcome events to retain the study blind and preserve the integrity of the clinical outcomes endpoint. These events will be selected as a "study event" on the AE eCRF and will be submitted for adjudication to the CEC as described in Section 7.5.

The Sponsor will consider the following list of clinical outcome events (Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) to be disease-related and exempt from being reported as an SAE and exempt from expeditious regulatory reporting, but will continue to report them in a non-expeditious manner: end-stage liver disease, liver transplant (preferred term: liver transplant), HCC (preferred term: hepatocellular carcinoma), variceal bleeding (preferred terms: gastroesophageal variceal hemorrhage, esophageal varices hemorrhage), hepatic encephalopathy (preferred term: hepatic encephalopathy) requiring hospitalization, spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), and ascites secondary to cirrhosis (preferred term: ascites).

The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event. The Sponsor is responsible for regulatory reporting of SAEs, including expeditious reporting of SUSARs, which are defined as SAEs that are considered related to the investigational product and considered unexpected.

7.2.3.10. Reporting Serious Adverse Events

Any SAE, including death due to any cause, occurring from the signing of the ICF through the end of study, regardless of relationship to the study treatment, must be reported immediately (without undue delay, under no circumstances later than 24 hours) by the investigator to Fortrea via entry in the eCRF.

The eCRF will collect data surrounding the SAE (eg, the nature of the symptom[s], time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued). The Investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic tests reports, and procedures as well as all pertinent medical information related to the event will also be collected in the eCRF.

Fortrea Patient Safety Services (PSS) will forward SAE queries requesting incomplete or missing information directly to the Investigator. It is the Investigator's responsibility to be diligent in providing this information back to Fortrea PSS as soon as it is available.

This study is utilizing an electronic data capture (EDC) system for data entry. In the event that the EDC system is unavailable for electronic SAE reporting, the manual back-up reporting procedures below should be followed:

- Complete an SAE Form
- Email (preferred) or fax the form to Fortrea at [redacted] or NA: [redacted]

When the EDC system becomes available, the EDC system should be updated with all previously reported information.

7.2.3.11. Pregnancy

Pregnancy is not reported as an AE unless there is a suspicion that an IMP may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported via entry in the eCRF. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Pregnancy must be reported in the same manner as an SAE as described in Section 7.2.3.10. If a pregnancy occurs during the study, study treatment must be discontinued immediately (or per Sponsor directive), and the pregnancy section of the eCRF completed. The study center should also complete the eCRF to document the outcome of the pregnancy (health of the neonate). In the event of a miscarriage, therapeutic abortion, death in utero, or if the pregnancy outcome leads to an SAE for the mother, follow the Procedure for Reporting an SAE (Section 7.2.3.10). In the event of a congenital anomaly, an SAE Form for the baby must be completed in the eCRF.

Any SAE occurring in association with a pregnancy that is brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study treatment must be promptly reported to Galectin Therapeutics Inc.

7.2.3.12. Central Clinical Laboratory Evaluations

Any abnormal laboratory test (hematology, clinical chemistry, urinalysis, or coagulation) including those that worsen from the baseline, considered to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

However, any clinically significant laboratory assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

Central laboratory tests are detailed in Appendix 3.

7.2.3.13. Alcohol Timeline Followback

The Alcohol TLFB is a drinking assessment method that obtains estimates of daily drinking and has been evaluated with clinical and nonclinical populations. Using a calendar, people provide retrospective estimates of their daily drinking over a specified time period that can vary up to 12 months from the interview date. Several memory aids can be used to enhance recall (eg, calendar; key dates serve as anchors for reporting drinking; standard drink conversion). The Alcohol TLFB has been shown to have good psychometric characteristics with a variety of drinker groups, and can generate variables that provide a wide range of information about an individual's drinking (eg, pattern, variability, and magnitude of drinking). Overall, the Alcohol TLFB method provides a relatively accurate portrayal of drinking, and has both clinical and research utility.

Current alcohol consumption will be assessed during the treatment phase using the Alcohol TLFB (Appendix 8). The Alcohol TLFB will be given to the patient at the beginning of the visit (Appendix 5), and will be considered source documentation.

Patients should be instructed to refrain from regular alcohol use during the study. If patients are found on the calendar to be drinking ≥7 standard alcohol drinks per week, they will be asked to stop drinking or reduce their intake. A sample Alcohol TLFB calendar along with instructions is provided in Appendix 8.

7.2.4. Standard Diet and Exercise Recommendations

Lifestyle modification is the foundation of treatment recommendations for NAFLD and NASH with or without hepatic fibrosis. Standard diet and exercise recommendations will be given by the Investigator as per standard, local practice and Investigator advice during SV1 and should be maintained throughout the study. The recommendations will be based on Therapeutic Lifestyle Change (TLC) counseling (or local equivalent) according to NCEP ATP III guidelines. The essential components of TLC and the macronutrient recommendations for the TLC diet are detailed in Appendix 11.

Assessment of dietary and lifestyle compliance will occur, at the timepoints in the schedules of assessments in Appendix 5, by asking the patient 2 questions to confirm if they have remained compliant to the diet and lifestyle recommendations "Have you remained compliant to the recommended diet since the last visit?" and "Have you remained compliant to the recommended physical activity since the last visit?". A yes/no response will be recorded in the eCRF.

7.3. Adverse Events

Definitions

An AE is any untoward medical occurrence or worsening of a preexisting medical condition in a patient or clinical investigation subject administered a pharmaceutical product (ie, study drug), which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom

or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE can arise from any use of the drug (eg, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. Note: A procedure is not an AE, but the reason for a procedure may be an AE.

A TEAE is defined as any event that meets the above-stated criteria after exposure to the IMP.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the patient signs the ICF and that is documented as part of the patient's medical history.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function, is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP).

Unexpected Adverse Event

An unexpected AE is one for which the nature or intensity of the event is not consistent with the applicable product information (eg, the IB).

Pretreatment Event

A pretreatment event is any untoward occurrence in a patient who has signed informed consent to participate in a study but before administration of any study drug. It does not necessarily have a causal relationship with study participation.

Reporting of Adverse Events

At each visit the Investigator, or delegate, will determine whether or not any AEs have occurred. Non-leading questions such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" should be used to elicit the patient to report any possible AEs. If any AEs have occurred, they will be recorded in the AE section of the eCRF and in the patient's source documents. If known, the diagnosis should be recorded, in preference to listing the individual signs and symptoms.

Adverse event reporting begins from the time of informed consent and ends 30 days after the last dose of study drug. However, SAEs judged by the Investigator to be related to the study drug

must be reported any time the Investigator becomes aware of such an event, even if this occurs more than 30 days after the last dose of the study drug. SARS-COV-2 (COVID-19) will follow the same AE/SAE reporting requirements as other AEs.

Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities.

Severity will be reported according to the NCI-CTCAE (v5.0). A grading (severity) scale is provided for each AE term. The NCI-CTCAE includes Grades 1 through 5, with unique clinical descriptions of severity for each AE based on the following general guidelines:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE.

Relationship to Study Treatment

The Investigator will make a determination of the relationship of the AE to the study drug according to the following guidelines:

- **Unrelated:**

  An AE for which sufficient information exists to indicate that the etiology is unrelated to the study drug. This category applies to those AEs that, after careful medical consideration, either are due to extraneous causes (eg, disease, environment) or are judged to be unrelated to the drug product under one of the following circumstances:

  - It does not follow a reasonable temporal sequence after administration of drug product
  - It could readily have been produced by the patient's clinical state or other modes of therapy administered to the patient
  - It does not reappear or worsen when the drug is re-administered

- **Related:**

  This category applies to those AEs that, after careful medical consideration, are thought to have a high degree of certainty of being related to the drug product or a connection with the drug product that cannot be ruled out An AE may be considered related if or when at least two of the following apply:

- It follows a reasonable temporal sequence after administration of the drug
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient
- It disappears or decreases on cessation or reduction in dose. Sometimes an AE does not disappear upon discontinuation of the drug, yet drug- relatedness clearly exists with re-exposure to drug

Event Outcome

Outcome of AEs will be classified as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

Note: In case of irreversible congenital anomalies the choice not recovered/not resolved should be used. "Fatal" should be used when death is possibly related to the reaction/event.

Action Taken for Adverse Events

The Investigator or designee will record the action taken for the AE in the eCRF. Dose modifications are not allowed (unless BMI changes). If the study drug was temporarily interrupted due to AE/SAE, the Investigator should discuss with the Medical Monitor any actions on re-introducing the study drug.

Actions taken will include:

- **Dose not changed**: The medication schedule was not changed.
- **Drug interrupted**: The medication schedule was modified by temporarily terminating the prescribed regimen of medication.
- **Drug withdrawn**: The medication schedule was modified through termination of the prescribed regimen of medication.
- **Not applicable**
- **Unknown**

Follow-up of Adverse Events

All (S)AEs that are ongoing at the time of discontinuation, or that develop prior to the final Follow-up Visit, will be followed for 30 days, or until resolution or stabilization.

Serious Adverse Events

An SAE is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life-threatening (see below)
- Requires patient hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Results in an important medical event (see below)

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A ***life-threatening AE*** is any AE that places the patient at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis of a more severe nature can be fatal. Hospitalization is to be considered only as an overnight admission.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating Investigator should not report hospitalization or prolongation of hospitalization in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (eg, stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (eg, elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

An additional exception to reporting SAEs will be hospitalizations for elective procedures that were anticipated or scheduled prior to study participation.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions (ie, the AE resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's bodily function/structure, physical activities, or quality of life).

If there is any doubt as to whether a case constitutes an AE or SAE based on the information available, the case should be treated as an SAE.

7.4. Safety Data Review

An independent DSMB will be established for the study. Details are provided in Section 8.5.1.

7.5. Clinical Events Committee

A blinded CEC will be convened to provide independent assessment of primary and secondary efficacy endpoints. Several committees, including the CEC, will adjudicate all the primary and some secondary endpoints (Section 2) events of DILI, HCC, and MACE (defined for this study as myocardial infarction, hospitalization for unstable angina, stroke/transient ischemic attack, and heart failure), as defined in the CEC Charter. The CEC assessment and adjudication will follow the procedures defined in the CEC Charter and will occur in a blinded, consistent, and unbiased manner throughout the course of the study to determine whether endpoints meet protocol-specified criteria. All CEC members will be independent of the participants in the study.

7.6. Pharmacokinetic Analysis

Plasma belapectin concentrations will be assayed in a minimum of 90 patients (with a minimum of 30 patients per treatment group) in Phase 2b. When a patient consents to PK collection, one patient will contribute PK blood samplings during the first 5 infusion visits (Visit 1, Visit 2, Visit 3, etc.) with blood sampling times at:

- Infusion Visit 1: pre-infusion (within 1 hour before the first infusion) and 3 hours after completing the first infusion
- Infusion Visit 2: 3 hours after the infusion and 24 to 48 hours after completing the second infusion
- Infusion Visit 3: 3 hours after the infusion and 3 to 4 days after completing the third infusion
- Infusion Visit 4: 3 hours after the infusion and 5 to 6 days after completing the fourth infusion
- Infusion Visit 5: pre-infusion sampling (within 1 hour before the infusion) and 3 hours after completing the fifth infusion.

The pre-infusion sample should be taken any time within 1 hour prior to the start of the infusion. All 3-hour samples during the infusion visits should be collected 3±1 hours after completing the infusion. The samples collected at 24 to 48 hours (2 days) should be collected any time between 24 and 48 hours after completing the second infusion. The blood sample collection on either of

the non-infusion visits (eg, Day 3, 4, 5, or 6) can occur any time during the specified day. The exact time of collection on the specific day should be recorded.

A maximum of 10 samples will be collected per patient. Every effort should be made to collect samples during the first 5 infusion visits. Flexibility will be allowed for patients to skip one PK sample if they cannot come exactly at the required time. If the plasma collection absolutely cannot occur, patients should contribute a minimum of 6 PK samples from any of the 3 infusion visits listed above (2 samples per visit).

Similar PK assessments will be repeated in a minimum of 60 patients (a minimum of 30 patients per treatment group) during Phase 3.

7.6.1. Sample Collection

All safety laboratory tests will be collected after the patient has been fasting for at least 8 hours. Each patient will have blood drawn for hematology, coagulation, and chemistry (including fasting insulin levels). Refer to the Study Manual for instructions for sample handling and shipping.

8. SAMPLE SIZE AND DATA ANALYSES

The objectives and endpoints for this study are described in Section 2. This section focuses on key aspects for the analysis and reporting of the primary, secondary, and exploratory efficacy, PK, and safety endpoints. The IA is also described in Section 8.7. The sample size rationale is also described in Section 3.1.2. Details for all endpoint analyses will be provided in the final SAP.

8.1. Determination of Sample Size

Assuming [redacted] patients ([redacted] patients per group) are enrolled in each treatment group in Stage 1 (Phase 2b), all patients on the optimal belapectin dose and placebo continue into Stage 2 (Phase 3), and an additional [redacted] new patients are enrolled and randomized (in a 2:1 ratio with [redacted] to the optimal belapectin dose and [redacted] to placebo, respectively), and also assuming an incidence rate of new varices of [redacted]%, and a [redacted]% patient dropout rate, then the study is estimated to provide at least [redacted]% power, with a 1-sided significance level of 0.[redacted], for detecting an annual relative risk reduction of [redacted]% for the primary efficacy endpoint (incidence of new varices) at 78 weeks (18 months) of treatment. Section 3.1.2 provides additional details about the sample size calculation.

With this planned sample size ([redacted] patients [redacted]] in the belapectin optimal treatment group and [redacted] [1[redacted]] in the placebo group), this study is estimated to provide at least [redacted]% power (1-sided significance level of [redacted]) for detecting a [redacted]% annual relative risk reduction in the key secondary efficacy endpoint (composite incidence of liver-related clinical outcome events, 78-week [18-month] cumulative rate), assuming an annual incidence rate as low as [redacted]%.[32]

The assumed yearly incidence rate of new varices of [redacted]% is based on data from a prior belapectin Phase 2 study (GT-026) in a subset of patients without esophageal varices at baseline who subsequently developed varices over 1 year of follow-up (mean rate = [redacted]%; [redacted] confidence interval [CI]: [redacted]%, [redacted]%). The actual incidence rate of new varices in this Phase 2b/3 study may be different. Therefore, to minimize the possibility of under-powering this trial, two adaptive modifications of the patient sample size are planned:

1) During Stage 1 (Phase 2b) when at least [redacted]% of patients complete 78 weeks (18 months) of treatment, a non-comparative (blinded) SSR procedure will occur. If the observed rate of new varices is less than was initially assumed, up to a maximum of [redacted] additional patients in each treatment arm may be enrolled without requiring a protocol amendment.

2) During the IA (to occur when all patients in Stage 1 [Phase 2b] have completed 78 weeks [18 months] of treatment), the sample size may also be adjusted to attain a CP [redacted] for the primary efficacy analysis.

Overall, the total number of patients enrolled in this trial (Phase 2b + Phase 3) may not exceed [redacted] without a protocol amendment.

8.2. Analysis Populations

The patients who are enrolled in the study are those who have signed the ICF. The following analysis populations for combined Phase 2b and Phase 3 data will be included for this study:

Full Analysis Set (FAS): [redacted]

Modified Full Analysis Set (mFAS): [redacted]

Per-protocol Set (PPS): [redacted]

Safety Set (SAF): [redacted]

PK Set: [redacted]

In addition, the following analysis populations will be defined for Phase 2b as supportive analyses:

Phase 2b FAS: [redacted]

Phase 2b SAF Set: [redacted]

[redacted]

8.3. General Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed with SAS software, version 9.4 or higher.

Descriptive statistics for continuous variables in summary tables will include the number of patients in the analysis (n), mean, SD, median, and range (minimum, maximum). Descriptive statistics for categorical variables in summary tables will include counts and percentages.

In general, statistical tests will be 2-sided at the significance level of [redacted] or one-sided with [redacted] unless otherwise specified. Two-sided [redacted]% CIs will be produced. Categorical endpoints will be summarized by the number and percentage with a [redacted]% CI for the percentage. Time-to-event endpoints will be summarized and displayed graphically using Kaplan-Meier (KM) method to estimate the median, and the 25th and 75th percentiles. Continuous endpoints with more than 1 post-baseline measurement will be analyzed using a Mixed Effects Model for Repeated Measures model.

Baseline is defined as the last assessment prior to infusion with study drug (ie, the pre-dosing assessment present in the database that is most proximate to the time of study drug administration). Measurements that are obtained after the first dose of study treatment will be considered post-baseline values. Change from baseline is defined as (post-baseline value – baseline value).

All data recorded on the eCRF will be provided in data listings showing individual patient values by treatment group and time of assessment, if applicable. Screen failure data will be captured in detail (by the procedure done).

Methods for dealing with missing data including dates, and analyzing efficacy and safety results will be specified in the SAP. Missing visits due to COVID-19 related logistics (site closures, patient quarantining, etc.) will be documented in the eCRF for reporting purposes.

8.3.1. Patient Demographics and Other Baseline Characteristics

The number and percentage of patients in the following disposition categories will be summarized by treatment group and overall:

- patients screened;
- screen failures and reasons for screen failure;
- patients included in the FAS, mFAS, PPS, SAF, Phase 2b FAS, and Phase 2b SAF;
- completed the study treatment;
- discontinued the study treatment and reasons for discontinuation;
- completed the study;
- discontinued study participation and reasons for discontinuation.

Demographic information: age, sex, race, ethnicity, height, weight, BMI, and other baseline measures such as liver stiffness, will be summarized by treatment group and overall, using descriptive statistics.

Randomized patients will be stratified by type 2 diabetes status.

8.3.2. Prior and Concomitant Therapy

All prior treatments for liver cirrhosis and NASH will be summarized by treatment group using variables as reported in the eCRF.

Other prior and concurrent medications, given to a patient from 30 days prior to Screening and throughout the entire duration of the patient's participation in the study, will be coded using the latest version of World Health Organization Drug Global Anatomic Therapeutic Chemical classification in the study, and tabulated by treatment group and overall, using counts and percentages, separately for:

- prior medications: medications discontinued prior to the start of exposure to study drug;
- concomitant medications: medications taken any time after the start of exposure to study drug.

Medications with a missing start date will be considered to have a start date before the first dose of study drug.

8.3.3. Study Drug Administration

Exposure to study drug and dosing compliance will be summarized using summary statistics.

The compliance will be summarized by treatment group, and is calculated using the actual number of dosing occasions at which study drug is administered, as a percentage of the planned number of dosing occasions.

8.4. Efficacy Analysis

8.4.1. Primary Efficacy Outcome Measures

The primary estimand is the proportion of patients (at 78 weeks [18 months]) who develop new esophageal varices in the FAS. The intercurrent events including treatment discontinuation and use of rescue therapy will be handled using the composite strategy. Estimands will be further defined in the SAP.

The global null hypothesis (H0) and alternative hypothesis (Ha) are:

H0: [redacted]

Ha: [redacted]

where p0 denotes the proportion (at 78 weeks [18 months]) of patients with development of esophageal varices in placebo group, and p1 and p2 denote the proportions in the 2 dose groups of belapectin. Suppose p1 is the proportion of the selected optimal dose group.

The individual null hypothesis and alternative hypothesis are:

H10: [redacted]

H20: [redacted]

The null hypotheses will be tested at a 1-sided significance level of [redacted]. The individual pvalue comparing the proportions between active dose groups of belapectin and placebo group will be

based on standardized test Z statistics for the difference of the proportions. For final analysis at the end of the study, the p-values obtained from both stages will be combined using the 'Inverse Normal' method to ensure the overall type I error is protected at the nominal level regardless of the type of design modifications (including sample size adjustment) at an IA. The 2-stage combined p-value will be calculated for each hypothesis as described above. In order to reject the H10 to claim the selected optimal dose is superior to placebo at the end of the study, both H10 and H0 must be rejected at the pre-specified 1-sided alpha level of [redacted]. The details of the testing procedures will be specified in the SAP.

The number and percentage (ie, proportion) of patients who develop esophageal varices up to 78 weeks (18 months) during Phase 2b and Phase 3 will be presented by treatment group in the FAS. The [redacted]% exact binomial CIs of the proportion and of the difference between each belapectin group and the placebo group will be estimated.

The supportive estimands include those similar to the primary estimand but defined in the mFAS and in the PPS and the proportion of patients (annual rate) who develop new esophageal varices in the FAS regardless of intercurrent events.

8.4.2. Secondary Efficacy Outcome Measures

The key secondary efficacy endpoint (composite events, in bullet list below) will be analyzed in the FAS as main analysis, and in the mFAS and PPS as supportive analysis:

- Cumulative incidence rate of patients in the belapectin treatment groups, compared to placebo, who develop any of the following:
    - varices (esophageal or gastric) requiring treatment
    - variceal bleed requiring hospitalization
    - clinically significant ascites requiring hospitalization
    - spontaneous bacterial peritonitis
    - overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization)
    - mortality (all-cause)
    - liver transplant
    - MELD score ≥15 on 2 consecutive occasions.

The cumulative incidence rate at 78 weeks (18 months) for a treatment group will be calculated as (number of patients with the event / total time at risk in weeks over all patients) * 78 weeks. The risk duration is from the first dosing date to the date of the first event. For patients who have no events reported, the risk duration is from the first dosing date to the end of follow-up in the study. The difference of the cumulative incidence rate at 78 weeks [18 months] between 2 groups, the associated [redacted]% CI and p-value will be calculated using the method proposed by Liu et al, 2006.[34]

The other secondary endpoints will be analyzed descriptively in the FAS including:

- Cumulative incidence rate at 78 weeks (18 months) of patients in the belapectin treatment groups who progress to large varices or develop red wales, compared to placebo

- Event-free survival by time to a first cirrhosis-related clinical event, including the following:
    - progression to large varices or red wales
    - esophageal variceal hemorrhage requiring hospitalization
    - clinically significant ascites requiring hospitalization
    - spontaneous bacterial peritonitis
    - overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization)
    - CTP score increase of ≥2 points (from baseline) on 2 consecutive occasions
    - MELD score to ≥15 as measured on 2 consecutive occasions
    - liver transplant
    - liver-related death.

Event-free survival will be analyzed using the KM method as described above.

Additional details are provided in the SAP.

8.4.3. Exploratory Efficacy Outcome Measures

The analyses of the exploratory endpoints will be performed descriptively in the FAS. The categorical endpoints will be summarized by the number and percentage with a [redacted]% CI for the percentage. Continuous endpoints with more than 1 post-baseline measurement will be analyzed using a Mixed Effects Model for Repeated Measures model.

An exploratory analysis of the proportion of patients who begin nonselective beta-adrenergic blocker treatment during the trial may be performed, and will be described in the SAP.

8.5. Safety Analysis

Safety variables include incidence of TEAEs, laboratory test results, vital signs, ECG results, and physical examination findings. All safety analyses for combined Phase 2b and Phase 3 will be based on the SAF, and in addition based on the Phase 2b SAF Set over Phase 2b and the extended period. No formal statistical analysis of the safety data will be performed. All safety data will be presented in patient data listings.

Adverse events will be coded using the latest version of MedDRA during the study, and classified as pretreatment or treatment-emergent as follows:

- Pretreatment AEs are defined as AEs that are reported or worsened after signing the ICF up to the first administration of study drug.

- TEAEs are defined as AEs that are reported or worsened on or after the first administration of study drug though the end of study.

The number and percent of patients with TEAEs, drug-related TEAEs, infusion procedure-related TEAEs, TEAEs of NCI-CTCAE Grade 3 or higher, TEAEs by severity, treatment-emergent SAEs (TESAEs), drug-related TESAEs, TEAEs leading to discontinuation

of the study treatment, and TEAEs leading to death will be presented by the treatment group in the overall summary, and also by MedDRA system organ class (SOC) and preferred term. The duration of the above TEAEs in days, from start to end, will be summarized as a continuous variable by treatment group.

The AE summary tables will include counts of patients. Therefore, if a patient experiences more than 1 episode of a particular AE, the patient will be counted only once for that event. If a patient has more than 1 AE that is coded to the same preferred term, the patient will be counted only once for that preferred term. Similarly, if a patient has more than 1 AE within an SOC, the patient will be counted only once in that SOC.

Actual values and change from baseline will be summarized by treatment group and visit using descriptive statistics (number of patients, mean, SD, and range [minimum – maximum]) for central clinical laboratory and vital signs measurements. Shift tables (low, normal, and high) between baseline and post-baseline timepoints will be presented by laboratory test and treatment group. The number and percentage of patients reporting markedly abnormal central clinical laboratory values will also be summarized by treatment group. Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries, but will be listed. Data obtained from laboratory tests not required by the protocol will not be summarized, but will be listed.

Descriptive statistics of ECG results and change from baseline at each visit will be presented by treatment group. Abnormal physical examination findings will be listed for each patient.

8.5.1. Data Safety Monitoring Board and Trial Steering Committee

A DSMB will be established that includes a panel of at least 3 independent experts, two physicians, and a statistician. A DSMB charter will be established. The primary role of the DSMB will be to periodically monitor the safety of the clinical study. The DSMB will meet at several predetermined times during the study and at any other times when it is determined by the study monitors or Principal Investigators that such a review is warranted. If more than 6 patients develop an SAE of NCI-CTCAE Grade 3 or 4 that the Investigator considers related to study drug, then the DSMB will evaluate trial data and consider recommendations on stopping the trial. An unblinded monitoring team will also be added to the study.

During the pre-specified IA after Phase 2b, the Phase 3 dose will be selected by the DSMB, and approved by the TSC (see below). The patient sample size may be adjusted based on a DSMB recommendation. The inclusion/exclusion criteria for Phase 3 will be reviewed by the DSMB as part of the IA, and may be modified (with approval of relevant IRBs/ECs) to ensure patient safety.

The Trial Steering Committee (TSC) is an executive decision-making group, with responsibility for overall supervision of this trial, considering the interests of the patients, investigators, and the Sponsor. The TSC Charter, approved by the Sponsor, details the roles, responsibilities, and TSC membership, which will include an experienced Chair and at least 2 independent members. The TSC will review the periodic safety reports from the DSMB. The TSC will review DSMB recommendations regarding adaptive trial modifications of the trial, including those arising from

the SSR in Phase 2b and also arising from the IA. The TSC may review the same IA data as the DSMB, under certain circumstances that are pre-defined in the DSMB Charter (eg, a DSMB recommendation to discontinue the trial) and according to pre-defined firewall procedures to ensure trial integrity.

8.6. Pharmacokinetic Analysis

Plasma levels of belapectin will be used to determine PK parameters (AUC, C_{max}, T_{max}, $t_{1/2}$). The potential influence of clinical characteristics (eg, age, sex, renal function, hepatic function, stage of cirrhosis, concomitant medications) on PK parameters will be evaluated. Further details will be included in a separate PK analysis plan.

8.7. Interim Analysis

The pre-planned IA is described in the study design in Section 3.1 (and Section 3.1.1 and Section 3.1.2), with further details provided in the SAP.

8.8. Mobile Clinical Services

Mobile clinical or home health services may be available for patient participation, within certain regions. This service, available to patients throughout Phases 2b and 3, is designed to ease the burden of this clinical trial's participation and to aid in patient retention. Many of the infusions can be conducted from the patient's home as well as certain assessments, including PK sub-study blood draws. Please consult the assigned study monitor for additional information and to determine if this service is approved for use in the region.

9. REFERENCES

1. Sanyal AJ. NASH: A global health problem. *Hepatol Res.* 2011;41:670-674.

2. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, and Wymer M. Fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;00:1-12.

3. Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol.* 2011;9:524-530.e1.

4. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*. 2011;140(1):124-31.

5. Misra VL, Khashab M, Chalasani N. Nonalcoholic fatty liver disease and cardiovascular risk. *Curr Gastroenterol Rep*. 2009;11: 50-55.

6. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global Epidemiology of non-alcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence and outcomes. *Hepatology*. 2016;64:73-84.

7. Caldwell S, Argo C. The natural history of non-alcoholic fatty liver disease. *Dig Dis*. 2010;28(1):162-8.

8. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2015: 00:1-12.

9. Haq I, Tripathi D. Recent advances in the management of variceal bleeding. *Gastroenterol Rep (Oxf)*. 2017;5(2):113-26.

10. Garcia-Tsao and Bosch. Management of varices and variceal hemorrhage in cirrhosis, N *Engl J Med*. 2010;362(9):823-32.

11. D'Amico Garcia-Tsao and Pagliaro. Natural history and prognosis indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44(1) :217-231.

12. D'Amico. Esophageal varices: from appearance to rupture; natural history and prognostic indicators. *Portal Hypertension in the 21st century*. 2004:147-54.

13. Groszmann RJ, Garcia-Tsao Bosch, Grace ND, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med.* 2005;353:2254-2261. doi: 10.1056/NEJMoa044456.

14. Franchis Robert de. Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *Journal of Hepatol*. 2015:63;743-752.

15. Garcia-Tsao G, Abraldes JG, Berzigotti A, and Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 Practice guidance by the American Association for the Study of Liver Disease. *Hepatology*. 2017;65(1):310-335.

16. Di LS, Sundblad V, Cerliani JP, et al. When galectins recognize glycans: from biochemistry to physiology and back again. *Biochemistry*. 2011;50(37):7842-7857.

17. Galactoarabino-Rhamnogalacturonate (GR-MD-02) Investigator Brochure, Version 5.0. 20 April 2019.

18. Traber PG, Chou H, Zomer E, et al. Regression of fibrosis and reversal of cirrhosis in rats by galectin inhibitors in thioacetamide-induced liver disease. *PLoS One*. 2013a;8(10):e75361. doi: 10.1371/journal.pone.0075361. eCollection 2013.

19. Traber PG, Zomer E. Therapy of experimental NASH and fibrosis with galectin inhibitors. *PLoS One*. 2013b;8(12):e83481. doi: 10.1371/journal.pone.0083481. eCollection 2013.

20. Chalasani N, Abdelmalek MF, Garcia-Tsao G, et al. Effects of belapectin, an inhibitor of galectin-3, in patients with nonalcoholic steatohepatitis with cirrhosis and portal hypertension. *Gastroentero*. 2020 Apr;158(5):1334-1345.

21. Ben-Menachem T, Decker GA, Early DS, et al. Adverse events of upper GI endoscopy. *Gastrointest Endosc*. 2012 Oct;76(4):707-718.

22. Wolfsen HC, Hemminger LL, Achem SR, et al. Complications of endoscopy of the upper gastrointestinal tract: a single-center experience. *Mayo Clin Proc*. 2004;79(10):1264.

23. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111(5):697-716.

24. Boyum JH, Atwell TD, Schmit GD, et al. Incidence and risk factors for adverse events related to image-guided liver biopsy. *Mayo Clin Proc*. 2016;91(3):329. Epub 2016 Feb 2.

25. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol*. 2010;8(10):877. Epub 2010 Apr 1.

26. West J, Card TR. Reduced mortality rates following elective percutaneous liver biopsies. *Gastroenterol*. 2010;139(4):1230.

27. Piccinino F, Sagnelli E, Pasquale G, et al. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. *J Hepatol*. 1986;2(2):165.

28. Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. *Ann Intern Med*. 1993;118(2):96.

29. Berzigotti A, Seijo S, Umberto Arena JG, et al. Elastography, spleen size and platelet count identify portal hypertension in patients with compensated cirrhosis. 2013;144(1):102–111.

30. Wong VW, Vergniol J, Wong GL, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology*. 2010;51(2):454-462.

31. Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol*. 2003;38(3):266-272.

32. Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepat*. 2019;0(0):1-15.

33. Janmahasatian S, Duffull SB, Ash S, et al. Quantification of lean bodyweight. *Clin Pharmacokinet*. 2005;44(10):1051-1065.

34. Liu GF, Wang J, Liu K, Snavely DB. Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. Statistics in Medicine. 2006;25:1275-1286.

35. Babor TF, Higgins-Biddle JC, Saunders JB, et al. AUDIT; The alcohol use disorders identification test: guidelines for use in primary care, 2nd ed. [Internet]. Geneva: World Health Organization; 2000 [cited 2013 Apr 30]. p. 31. Available from: http://www.who.int/substance_abuse/activities/sbi/en/

36. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145(4):247-254.

37. Bhardwaj A, Joshi S, Sharma R, Bhardwaj S, Agrawal R, Gupta N. QTc prolongation in patients of cirrhosis and its relation with disease severity: An observational study from a rural teaching hospital. *J Family Med Prim Care*. 2020;9(6):3020-3024.

38. Hung CS, Tseng PH, Tu CH, et al. Nonalcoholic Fatty Liver Disease Is Associated With QT Prolongation in the General Population. *J Am Heart Assoc*. 2015 Jul 21;4(7):e001820. doi: 10.1161/JAHA.115.001820.

39. Țieranu E, Donoiu I, Istrătoaie O, et al. Q-T Interval Prolongation in Patients with Liver Cirrhosis. *Curr Health Sci J*. 2018 Jul-Sep;44(3):274-279. doi: 10.12865/CHSJ.44.03.11. Epub 2018 Jul 15.

10. APPENDICES

Appendix 1 – Protocol Revision History

This version supersedes [redacted]

The major revisions for [redacted]

- Protocol version date, version number, and superseded versions listing are updated.
- The new EU trial number is added for the transition application.
- Sponsor Signatory is updated to [redacted]
- Update to ***Objectives and Endpoints: Key Secondary Efficacy Endpoint*** (synopsis), ***Statistical Methods: Secondary analysis*** (synopsis), Section ***2. Objectives and Endpoints***, and Section ***8.4.2. Secondary Efficacy Outcome Measures*** includes the addition of "on 2 consecutive occasions" following "model for end-stage liver disease (MELD) score ≥15" or "MELD score ≥15" to match the changes already made to the protocol during last amendment for consistency.
- Update to ***Objectives and Endpoints: PK Objective*** (synopsis) and Section ***2. Objectives and Endpoints*** includes the revision of PK objective from "To determine the single-dose and steady-state pharmacokinetic (PK) profile of belapectin" to "To produce a population PK model of belapectin".
- Update to ***Statistical Methods: Primary analysis*** (synopsis) and Section ***8.4.1. Primary Efficacy Outcome Measures*** includes the removal of the sentence "If a patient discontinues the study treatment and has a missing EGD evaluation at the Early Termination Visit, the estimand takes these cases as the worst outcome in combination with the clinically adjudicated development of new esophageal varices.", which is updated and more comprehensively described in SAP.
- Updates to Section ***3.1.2. Sample Size and Decision Rules - Initial Patient Sample Size Estimates*** include
  - the revision from "1" to "I" for the term Type I error, the revision from "4. The efficacy boundary: Adjusted p-value=[redacted]" [redacted] The efficacy boundary: Adjusted p-value = [redacted]
  - the revision from "6. Information fraction at the IA = [redacted] to "[redacted] Information fraction at the IA = [redacted]
  - the revision to specify the method used to compute the adjusted p-value for multiplicity adjustment.

- Updates to Section ***3.1.2. Sample Size and Decision Rules - Interim Analysis Decision Rules and Sample Size Re-estimation*** include
  - the revision from "That probability will be evaluated under the assumption that the treatment difference …" to "That CP will be calculated under the assumption that the true underlying treatment difference …"
  - the revision from "If the adjusted p-value at IA ≤ [redacted], then the trial will be stopped for overwhelming efficacy" to "If at least one of the null hypotheses corresponding to the comparisons of the belapectin doses versus placebo can be rejected using the closed testing approach at IA using the alpha-level [redacted] for the comparison of primary efficacy, stop the trial for efficacy"
  - the removal of "If the adjusted p-value at IA ≥ [redacted], then the trial will be stopped for futility"
  - the revision from "If CP < [redacted], stop the trial after IA" to "If CP < [redacted] (Futility/Unfavorable zone), stop the trial after IA for futility"
  - the revision from "If 0.1 ≤ CP < [redacted]" to "If [redacted] ≤ CP < [redacted] (Promising zone)"
  - the revision from "If CP ≥ [redacted]" to "If CP ≥ [redacted] (Favorable zone)"
  - the removal of the paragraph "These calculations will be performed using the EAST software (version 6.5, Cytel) sample size re-estimation and trial monitoring modules. For final analysis, the p-values obtained from both the stages will be combined using the "Inverse Normal" method. This general approach is commonly used to construct adaptive designs in confirmatory trials and guarantees that the overall Type I error rate in this trial is protected at the nominal level regardless of the type of design modifications at the IA, including decisions to adjust the sample size. Detailed sample sizes, interim monitoring, and simulations outputs will be from EAST software (version 6.5, Cytel)."

- Update to Section ***7.2.1.4. Esophagogastroduodenoscopy Evaluation*** includes the addition of "days" following "14" for clarity.

- Update to ***Appendix 5 – Schedule of Assessments, Table 5*** and ***Table 7,*** footnote **l**. includes the revision from "within approximately 2 weeks after the Week 78 visit or study discontinuation" to "within approximately 2 weeks of the Week 78 visit or study discontinuation" to match the description in protocol Section 7.2.1.4 for consistency and accuracy.

- Editorial changes are made for consistency and accuracy.

Appendix 2 – Non-Alcoholic Steatohepatitis Cirrhosis Definition

Definitive	Probable	Possible
1a. Current biopsy shows cirrhosis with steatohepatitis. There is no evidence for a competing etiology[a]. OR 1b. Previous biopsy showed steatohepatitis, but now with cirrhosis, either by clinical or imaging, or biopsy. If there is a current biopsy, it does not show evidence of steatosis or steatohepatitis as the histological lesions may have burnt out. There is no evidence for a competing etiology[a]. There is at least one co-existing or history of metabolic comorbidity[b] to corroborate a diagnosis of NAFLD. OR 1c. Current biopsy shows cirrhosis with steatosis. There is no evidence for a competing etiology[a]. There are at least two co-existing or history of metabolic comorbidities[b] with obesity[c] or diabetes being one of them to corroborate a diagnosis of NAFLD.	2a. Previous biopsy shows steatosis, but now with cirrhosis, either by clinical, or imaging[d], or biopsy. If there is a current biopsy, it does not show evidence of steatosis or steatohepatitis as histological lesions may have burnt out. There is no evidence for a competing etiology[a]. There are at least two co-existing or history of metabolic comorbidities[b] with obesity[c] or diabetes being one of them to corroborate a diagnosis of NAFLD. OR 2b. Patient with cirrhosis with current or previous imaging[d] showing steatosis. There is no liver histology available. There is no evidence for a competing etiology[a]. There are at least two co-existing or history of metabolic comorbidities[b] with obesity[c] or diabetes being one of them to corroborate a diagnosis of NAFLD. OR 2c. "Cryptogenic cirrhosis" without current or previous evidence of steatosis by imaging[d] or by histology. There is no evidence for a competing etiology[a] <u>but</u> there are at least two co-existing or history of metabolic comorbidities[b] with obesity[c] or diabetes being one of them to corroborate a diagnosis of NAFLD.	3a. "Cryptogenic cirrhosis" without current or previous evidence of steatosis by imaging or by histology. There is no evidence for a competing etiology[a] <u>but</u> there is at least one co-existing or history of metabolic comorbidity[b], with either obesity[c] or diabetes. OR 3b. Patients with previously eradicated hepatitis C virus, or remote history of heavy alcohol consumption, but currently have evidence of cirrhosis and histological evidence of steatohepatitis.

NAFLD = non-alcoholic fatty liver disease.
[a] Competing etiology: including alcohol, viral hepatitis, hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alpha-1-antitrypsin deficiency and autoimmune hepatitis
[b] Comorbidities include: history of diabetes, hypertension, dyslipidemia or obesity. We suggest a duration of at least 5 years however this can be discussed per study protocol.
[c] Body mass index ≥30 kg/m^2 or central obesity per consensus guidelines
[d] Such as FibroScan or other methods to be discussed with the Medical Monitor on a case-by-case basis

Appendix 3 – Central Clinical Laboratory Evaluations

The following central clinical laboratory analytes will be assessed:

Chemistry	**Hematology**	**Other Tests (Serology)**
Albumin	Hematocrit	Hepatitis A antibody (IgM)
ALP	Hemoglobin	Hepatitis B core antibody
ALT	Platelet count	Hepatitis B surface antibody
AST	Red blood cell (RBC) count	Hepatitis B surface antigen
Blood urea nitrogen	Red cell indices (MCV, MCH, MCHC)	Hepatitis C antibody
Calcium	White blood cell (WBC) count	HIV antibody
Chloride	WBC differential	
Bicarbonate	(% and absolute):	**Drug Screen (Urine)**
Creatinine	Basophils	Amphetamines
Fasting insulin level	Eosinophils	Cocaine (metabolite)
GGT	Lymphocytes	Non-prescription opiates
Glucose	Monocytes	Barbiturates
Lactate dehydrogenase	Neutrophils	Benzodiazepines
Magnesium		Marijuana/Cannabinoids (THC)*
Phosphorus	**Coagulation**	Methadone
Potassium	Prothrombin time	Methamphetamine
Sodium	Partial thromboplastin time	Methylenedioxymethamphetamine
Total and direct bilirubin	INR	Opiates
		Phencyclidine
Total protein		
Uric acid	**For Women of Childbearing Potential Only**	
HbA1c	Urine and serum pregnancy test	
Triglycerides		
HDL-C		

Urinalysis	
Color	Follicle-stimulating hormone testing (for post-menopausal females only)
Blood	
Clarity	
Bilirubin	
pH and specific gravity	
Leukocyte esterase	
Glucose	
Hyaline and other casts	
Ketones	
Bacteria	
Nitrite	
Epithelial cells	
Protein	
Crystals	
Microscopic (including RBCs and WBCs)	
Yeast	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; IgM = immunoglobulin M; INR = International normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; THC = tetrahydrocannabinol; WBC = white blood cell.
*Marijuana/Cannabinoids (THC) is not an automatic exclusion, but rather should be based upon local requirements where applicable.

Appendix 4 – Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Ethics Committee (EC) by the Investigator and reviewed and approved by the IRB/EC before the study is initiated.

- Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each patient will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Patients will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Patients will be given an opportunity to ask questions about the study prior to providing consent for participation.

Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The patient will be given a copy of the signed ICF, and the original will be maintained with the patient's records.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

Emergency Medical Support and Patient Emergency Card

Patients included in this study will be provided with a Patient Emergency Card at Infusion Visit 1. The Patient Emergency Card is based on the need to provide patients with a way of identifying themselves as participating in this study, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the patient's medical treatment.

This card is designed to provide information to health care providers who are not part of the clinical study; this may include the possibility of emergency unblinding if needed, in case of blinded studies. The Investigators, who are already aware of the protocol and treatment, have other means of accessing necessary medical information for the management of emergencies occurring in their patients.

The first point of contact for all emergencies will be the Investigator caring for the affected patient. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, he/she will answer any questions. Any subsequent action (eg, unblinding) will follow the standard processes established for the Investigators.

Patient Data Protection

Patients will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Patient and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual patients or Investigators will be redacted according to applicable laws and regulations.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient. The patient must also be informed that his/her medical records may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, appropriate IRB/EC members, and inspectors from regulatory authorities.

Independent Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established that includes a panel of at least 3 independent members to include two medical experts and a statistician. An official DSMB

charter will be established and approved by all members and Galectin Therapeutics Inc. The primary role of the DSMB will be to periodically monitor the safety of the clinical study. The DSMB will meet at several predetermined times during the study and at any other time when it is determined by the study monitors or Principal Investigators that such a review is warranted. An organizational meeting will be held prior to the first patient randomly assigned to investigational medicinal product (IMP) to review and approve the DSMB Charter and to review the outputs (Data, Tables, Listings and Figures) to be provided to the DSMB for scheduled reviews. In addition, an unblinded monitoring team will be established. If more than 6 patients develop a serious adverse event of National Cancer Institute-Common Terminology Criteria for Adverse Events Grade 3 or 4 that is considered by the Investigator to be related to IMP, then the DSMB shall evaluate the trial data and consider recommendations on stopping the trial.

The investigative study center staff, patients, the Sponsor and its representatives, and representatives of the CRO, except those responsible for providing unblinded data to the DSMB, will remain blinded throughout the full duration of the study until after the database is locked at the conclusion of the blinded treatment period.

Trial Auditing

Regulatory authorities, IRB/EC, and/or Galectin Therapeutics Inc. or its designee(s) may request access to all source documents, eCRF data, and other study documentation for on-site or remote audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

It is understood that all patient-specific information is confidential and no documentation that can link study information to the specific patient will be collected or retained by the Sponsor.

Trial Monitoring

A Sponsor representative will visit the site at regular intervals and as managed under the risk-based monitoring approach, which is considerate of onsite source document verification and remote review (no source) options. Available medication dispensing and clinical drug supply records will be verified by the study monitor. It is understood that all patient specific information is confidential and that no documentation that can link study information to the specific patient will be collected or retained by the Sponsor. Remote source document verification may only occur under approved country regulations and patient consent. Remote source document verification solutions may include encrypted email, remote access to the electronic medical record, video calls, or teleconferences with the Investigator.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All patient data relating to the study will be recorded on eCRFs. The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.
- Fortrea or a designee of the Sponsor is responsible for the data management of this study including quality checking of the data. Pre-defined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 15 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, patient-specific study data will be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion. All data generated from external sources (eg, central laboratory, pharmacokinetics, pharmacodynamics, and electrocardiogram central readers) and transmitted to the designee electronically will be integrated with the patient's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each patient who signs an ICF and undergoes any Identification of Patients or Screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA) and approval of the Sponsor, which will not be unreasonably withheld. Unless otherwise specified in the CSA, the following process shall occur:

The institution and Investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor shall have 60 days to respond with any requested revisions, including (without limitation) the deletion of confidential information. The Investigator shall act in good faith upon requested revisions, except the Investigator shall delete any confidential information from such proposed publications. The Investigator shall delay submission of such publication or presentation materials for up to an additional 90 days in order for the Sponsor to have a patent application(s) filed.

Appendix 5 – Schedule of Assessments

Table 3 NAVIGATE Schedule of Assessments – Identification of Patients and Screening for Stage 1 (Phase 2b) and Stage 2 (Phase 3)

Procedure			
Week	**Week -10 to Day -1[a]**		
All Phase 2b and newly enrolled Phase 3 patients	**SV1[a]**	**SV2[a]**	**SV3[a]**
Informed consent (for Phase 2b and for new patients entering Phase 3)[b]	X		
IWRS[c]	X		
Demographic information, medical, surgical, and medication history	X		
Inclusion/exclusion criteria	X		X[q]
Complete physical examination	X		
Vital sign measurements (heart and respiratory rate, BP, and body temperature)[d]	X	X	X[q]
Weight, height and BMI	X		
Historical NASH cirrhosis confirmation[e]	X		
Liver biopsy (unless a historic liver biopsy had been performed, a historic liver biopsy is acceptable but the biopsy blocks and/or slides must be available for central review if this is the main/only confirmation being used for evidence of NASH cirrhosis)[f]		X	
Assessment of cirrhosis complications	X		
12-lead ECG	X		
Chest radiographs (posterior-anterior and lateral views) [t] (not to be performed in Germany)	X		
HCC assessment (ultrasound or CT or MRI within 6 months prior to randomization)[g]	X[s]		
Liver and abdomen ultrasound (to assess for HCC and ascites)[g]	X[s]		
Assessment of spleen size by imaging (ultrasound, MRI, or CT scan) [h, r]	X[s]		
FibroScan (transient elastography)[i]	X		
Assessment of abdominal collateral circulation (ultrasound, MRI, or CT scan or physical exam)[j, r]	X[s]		
Hematology[k] and blood chemistry[l]	X		
Liver function testing (ALT, AST, bilirubin, ALP)[l]	X	X	X (required if SV1 and SV2 results are different >33%)[m]
Coagulation profile (including INR)[l]	X	X[n]	
Viral hepatitis A, hepatitis B, and hepatitis C serology	X		
HIV serology	X		
Serum pregnancy test (females of childbearing potential only)	X		
Follicle-stimulating hormone testing (for post-menopausal females only)	X		
Urine drug screen (amphetamines, cocaine, and non-prescription opiates)	X		
Urine pregnancy test (females of childbearing potential only)	X		X[q]
Urinalysis[o]	X		
EGD (upper gastrointestinal endoscopy) with video[p]		X	

Procedure			
Week	**Week -10 to Day -1[a]**		
All Phase 2b and newly enrolled Phase 3 patients	**SV1[a]**	**SV2[a]**	**SV3[a]**
Alcohol TLFB	X		
Alcohol Use Disorder Identification Test	X		
MELD Score	X		
CTP Score	X		
AE monitoring	X	X	X[q]
Diet and exercise recommendations	X		

Abbreviations: AE = adverse Event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; CT = computed tomography; CTP = Child-Turcotte-Pugh; ECG = electrocardiogram; EGD = esophagogastroduodenoscopy; HCC = hepatocellular carcinoma; HIV = human immunodeficiency virus; INR = international normalized ratio; IWRS = interactive web response system; MELD = model for end-stage liver disease; MRI = magnetic resonance imaging; NASH = non-alcoholic steatohepatitis; SV = Screening Visit; TLFB = timeline followback.

a. The Screening Visit window is up to 10 weeks. Patients who fail to meet eligibility criteria during the screening period due to an abnormal central laboratory result may undergo retesting of the abnormal central laboratory parameter during the screening window and at the discretion of the Investigator. Screening Visits 2 and 3 are designated for the purposes of baseline transaminase assessment. Screening Visit 2 should occur 2 to 4 weeks after SV1. Screening Visit 3 must occur within 2 weeks after SV2 and prior to randomization in those patients who require additional chemistry due to variability. Note: It is not required for all of the assessments above to be performed on the same day. All appropriate steps should be taken to ensure study-related assessments are completed and results available within the 10-week screening period, with the exception of delays in laboratory results (including biopsy) and EGD reporting, which were not due to site delays in performing these examinations.
b. Patients can be consented for the entire study (Phase 2b/3, Stage 1 and 2) at the start without re-consent at Phase 3 for patients continuing between phases.
c. If, at any time during the Screening period, the patient fails to meet Screening requirements, IWRS should be registered with a patient status change of “Screen Failure” in real time.
d. Vital sign measurements include heart and respiratory rate, BP, and body temperature. Blood pressure will be obtained with the patient in the seated position.
e. Patients who have had a previous liver biopsy with a diagnosis of NASH cirrhosis as per the Liver Forum definition are eligible to move forward to Screening.
f. When a biopsy is utilized for inclusion, results from the central study pathologist must be available before the patient is randomized.
g. Liver and abdomen ultrasound is not needed if there is a valid documentation of the ultrasound, MRI, or CT scan for HCC and ascites within a 6 months window. If no historical images to assess HCC and ascites within 6 months of randomization is available, then a screening ultrasound should be done.
h. Spleen size can be measured at any time point within the screening period, but prior to the liver biopsy (if the biopsy is needed). If there is a valid documented spleen size available from medical history, this measure can be used for eligibility. The evaluation of spleen size can be combined with the evaluation of abdominal collateral circulation.
i. FibroScan (transient elastography) can be done at any time point within the screening period, but prior to the liver biopsy (if the biopsy is needed). If there is a valid historical FibroScan evaluation is available from medical history, this measure could be used for eligibility assessment. If a historical FibroScan was used at screening, then a Baseline FibroScan evaluation should be done at Infusion Visit 1. If the Inclusion Criterion 3 was confirmed by either platelets level (ie, Inclusion Criterion 3a) or by HVPG (ie, Inclusion Criterion 3b), then a FibroScan should still be conducted during the screening to obtain the baseline level for the study.
j. Abdominal imaging for the assessment of abdominal collateral circulation can be performed by ultrasound, MRI, or CT scan, or evidence of abdominal collateral circulation can be confirmed by caput medusae seen upon physical examination. This evaluation can be combined with the evaluation of spleen size. If there is a valid documented presence of abdominal collateral circulation available from medical history, this measure can be used for eligibility. If, during Screening, the evaluation of abdominal collateral circulation has been performed at the same time as the evaluation of spleen size, it will not have to be repeated.
k. Hematology will include complete blood cell count with differential (red blood cells, white blood cells, red cell indices, platelets, hemoglobin, and hematocrit).
l. Blood chemistry will include ALT, AST, albumin, ALP, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, gamma-glutamyl transferase, and fasting insulin level. Patients must be in a fasted state for at least 8 hours prior to blood collection. Please refer to Section 4.4.4.1 for testing at SV2 and SV3 visits (where required).
m. Please see Section 4.4.4.1 for details and for calculating the Baseline values.
n. INR will be tested at both SV1 and SV2 as per Section 4.4.4.1.

o. Urinalysis will include bacteria, bilirubin, blood, crystals, color, clarity, epithelial cells, glucose, hyaline and other casts, leukocyte esterase, nitrite, pH, specific gravity, ketones, protein, red blood cells, white blood cells, and yeast.
p. Esophagogastroduodenoscopy must include high resolution videos and will be centrally read. Patients will undergo an EGD with video documentation during screening. The EGD for re-screened patients could be acceptable if within 6 months prior to randomization to verify the inclusion criteria.
q. These SV3 assessment/tests are only required if SV3 takes place. For SV3 requirement, please refer to footnote a.
r. The assessment of spleen size and/or abdominal collateral circulation are only mandatory to support Inclusion Criterion 3c verification (ie, for patients who do not meet Inclusion Criterion 3 confirmation by platelets level [ie, Inclusion Criterion 3a] or/and by HVPG [ie, Inclusion Criterion 3b] historical measurement). If Inclusion Criterion 3c is required, then either historical images (no timeframe limit) or screening images are acceptable. If a patient meets Inclusion Criterion 3 by platelets level or historical record of platelet level (ie, Inclusion Criterion 3a) or/and by HVPG level (ie, Inclusion Criterion 3b), then it is recommended to record the historical data for the spleen size and abdominal collateral circulation, only if available.
s. Can be done at either SV1 or SV2 or at any time during the Screening period.
t. Screening Chest Radiographs will not be completed for patients participating in Germany due to local regulations.

Table 4 NAVIGATE Schedule of Assessments – Randomization and Treatment Phase: Stage 1 (Phase 2b) – Weeks 0 to 52

Infusion Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Week ± 3 days	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Day number	**0**																										
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLDQ[a]	X																										
Alcohol TLFB[a]	X				X				X				X				X				X				X		
Vital sign measurements and BMI[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limited physical examination[c]	X		X				X						X						X						X		
Assessment of cirrhosis complications[d]	X		X				X						X												X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of dietary and lifestyle recommendation	X						X						X						X						X		
Urine pregnancy test[e]	X		X		X		X		X		X		X		X		X		X		X		X		X		X
Urinalysis (dipstick)	X						X						X						X						X		
12-lead ECG	X												X												X		
Hematology[f]	X						X						X						X						X		
Blood chemistry[g]	X						X						X						X						X		
Coagulation profile (including INR)	X						X						X						X						X		
Serum sample for [redacted] test[h]	X													X													X
Plasma/serum samples for storage, for future biomarkers and gene expression analysis[h] (optional testing)	X													X													X
Liver stiffness assessment (FibroScan)[i]	X[j]													X													X
Liver and abdomen ultrasound (for HCC and ascites)	X[j]												X												X		
MELD Score	X						X						X						X						X		

Infusion Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Week ± 3 days	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Day number	**0**																										
CTP Score	X						X						X						X						X		
IMP administration[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample (subset of patients)[l]	X	X	X	X	X																						
Patient emergency card dispensing	X																										

Abbreviations: AE = adverse event; BMI = body mass index; CLDQ = chronic liver disease questionnaire; CTP = Child-Turcotte-Pugh ; ECG = electrocardiogram; [redacted]; HCC = hepatocellular carcinoma; IMP = investigational medicinal product; INR = international normalized ratio; IWRS = interactive web response system; MELD = model for end-stage liver disease; PK = pharmacokinetic; TLFB = timeline followback.

a. To be administered at the beginning of the visit.
b. Vital sign measurements include heart and respiratory rate, blood pressure, and body temperature prior to IMP administration. Blood pressure will be obtained with the patient in the seated position. Body mass index calculated from body weight and height. Height is measured during Screening Visit 1 only, and that height will be used for all subsequent BMI calculations.
c. Limited physical examination includes examination of the heart, lung, and abdomen.
d. Esophageal hemorrhage, clinically significant ascites requiring hospitalization, overt hepatic encephalopathy, listing for liver transplant, liver transplant, or liver-related death.
e. Urine pregnancy test will be given to females of childbearing potential every 4 weeks during the treatment phase.
f. Hematology will include complete blood cell count (red blood cells, white blood cells, red cell indices, platelets, hemoglobin, and hematocrit) with differential.
g. Blood chemistry will include alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, gamma-glutamyl transferase, and fasting insulin level. Patients must be in a fasted state (at least for 8 hours) prior to blood collection.
h. [redacted].
i. Within 14 to 28 days after the final dose of IMP or where feasible following study termination due to the occurrence of a clinical event or withdrawal of consent. Whenever possible, patients who are terminated from the study, regardless of visit, should also have all the post-study evaluations performed including esophagogastroduodenoscopy and FibroScan.
j. If an HCC and ascites assessment was performed at Screening, the assessment does not need to be repeated at Infusion Visit 1. If a historical (within 6 months) assessment of HCC and ascites was used at Screening, then a new assessment should be performed at Infusion Visit 1. If FibroScan was done at Screening, it will not need to be repeated at Infusion Visit 1. If a historical FibroScan was used for eligibility, then a baseline FibroScan should be done at Infusion Visit 1.
k. Investigational medicinal product administration will occur after the following procedures: limited physical examination, vital sign measurements, hematology, blood chemistry, biomarker blood samples, and FibroScan.
l. For patients who consent to PK sampling, samples will be collected any time within 1 hour before the first infusion and at 3±1 hours after completing the infusion, 3±1 hours and any time between 24 to 48 hours after completing the second infusion, 3±1 hours and any time 3 to 4 days after completing the third infusion, 3±1 hours and any time 5 to 6 days after completing the fourth infusion, and any time within 1 hour before the fifth infusion and 3±1 hours after completing the infusion. A maximum of 10 samples will be collected per patient. If the 10 plasma samples absolutely cannot occur, the patient should contribute a minimum of 6 PK samples (2 samples per visit) from any of the 3 of the first 5 infusion visits.

Table 5 NAVIGATE Schedule of Assessments – Randomization and Treatment Phase: Stage 1 (Phase 2b) – Weeks 54 to 78

Infusion Visit	28	29	30	31	32	33	34	35	36	37	38	39	40	Early Termination[a]	EOS[a]
Week ± 3 days	54	56	58	60	62	64	66	68	70	72	74	76	78	14-28 days after the last dose[a]	14 days after Early Termination Visit[a]
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLDQ[b]														X	X
Alcohol TLFB[b]		X				X				X			X	X	X
Vital sign measurements and BMI[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limited physical examination[d]				X			X						X	X	X
Assessment of cirrhosis complications[e]				X									X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of dietary and lifestyle recommendation				X						X			X	X	X
Urine pregnancy test[f]		X		X		X		X		X		X	X	X	X
Urinalysis (dipstick)						X							X	X	X
12-lead ECG													X	X	X
Hematology[g]						X							X	X	X
Blood chemistry[h]						X							X	X	X
Coagulation profile (including INR)						X							X	X	X
Serum sample for [redacted] test[i]													X	X	
Plasma/serum samples for storage, for future biomarkers and gene expression analysis[i] (optional testing)													X	X	
Liver stiffness assessment (FibroScan)[j]													X	X	
Liver and abdomen ultrasound (for HCC and ascites)													X	X[k]	X
MELD Score						X							X	X	X
CTP Score						X							X	X	X
EGD (upper gastrointestinal endoscopy) with video[l]													X	X[k]	
IMP administration[m]	X	X	X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: AE = adverse event; BMI = body mass index; CLDQ = chronic liver disease questionnaire; CTP = Child-Turcotte-Pugh; ECG = electrocardiogram; EGD = esophagogastroduodenoscopy; [redacted]; EOS = end of study; HCC = hepatocellular carcinoma; IMP = investigational medicinal product; INR = international normalized ratio; IWRS = interactive web response system; MELD = model for end-stage liver disease; TLFB = timeline followback.

a. Visits performed only for patients who are not continuing into Stage 2 (Phase 3) of the study. Patients continuing into Stage 2 (Phase 3) will complete Stage 1 (Phase 2b) Infusion Visit 40 (Week 78) and then Stage 2 (Phase 3) Infusion Visit 1 which should take place 2 weeks after Infusion Visit 40 (Week 78).
b. To be administered at the beginning of the visit.
c. Vital sign measurements include heart and respiratory rate, blood pressure, and body temperature prior to IMP administration. Blood pressure will be obtained with the patient in the seated position. Body mass index calculated from body weight and height. Height is measured during Screening Visit 1 only, and that height will be used for all subsequent BMI calculations.
d. Limited physical examination includes examination of the heart, lung, and abdomen.
e. Esophageal hemorrhage, clinically significant ascites requiring hospitalization, overt hepatic encephalopathy, listing for liver transplant, liver transplant, or liver-related death.

f. Urine pregnancy test will be given to females of childbearing potential every 4 weeks during the treatment phase.
g. Hematology will include complete blood cell count (red blood cells, white blood cells, red cell indices, platelets, hemoglobin, and hematocrit) with differential.
h. Blood chemistry will include alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, gamma-glutamyl transferase, and fasting insulin level. Patients must be in a fasted state (at least for 8 hours) prior to blood collection.
i. [redacted]
j. Within 14 to 28 days after the final dose of IMP or where feasible following study termination due to the occurrence of a clinical event or withdrawal of consent. Whenever possible, patients who are terminated from the study, regardless of visit, should also have all the post-study evaluations performed including EGD with video recording documentation and FibroScan.
k. The assessment should not be repeated if previously performed at Infusion Visit 40 (Week 78).
l. Esophagogastroduodenoscopy is to be completed within approximately 2 weeks of the Week 78 visit or study discontinuation regardless of which visit discontinuation occurs. Esophagogastroduodenoscopy must include high resolution videos and will be centrally read.
m. Investigational medicinal product administration will occur after the following procedures: limited physical examination, vital sign measurements, hematology, blood chemistry, biomarker blood samples, EGD with video recording documentation, and FibroScan.

Table 6 NAVIGATE Schedule of Assessments –Treatment Phase: Stage 2 (Phase 3) – Weeks 0 to 52[a]

Infusion Visit	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Week ± 3 days	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Day number	**0**																										
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLDQ[c]	X																										
Alcohol TLFB[c]	X				X				X				X				X				X				X		
Vital sign measurements and BMI[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limited physical examination[e]	X						X						X						X						X		
Assessment of cirrhosis complications[f]	X						X						X						X						X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of dietary and lifestyle recommendation	X						X						X						X						X		
Urine pregnancy test[g]	X		X		X		X		X		X		X		X		X		X		X		X		X		X
Urinalysis (dipstick)	X						X						X						X						X		
12-lead ECG[b]	X												X												X		
Hematology[h]	X						X						X						X						X		
Blood chemistry[i]	X						X						X						X						X		
Coagulation profile (including INR)	X						X						X						X						X		
Serum sample for [redacted]	X													X													X
Plasma/serum samples for storage, for future biomarkers and gene expression analysis[b, j] (optional testing)	X[k]													X													X

Infusion Visit	**1**[b]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Week ± 3 days	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Day number	**0**																										
Liver stiffness assessment (FibroScan)[b, l]	X[k]													X													X
Liver and abdomen ultrasound (for HCC and ascites)[b, j]	X[k]												X												X		
MELD Score	X						X						X						X						X		
CTP Score	X						X						X						X						X		
IMP administration[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample (subset of patients)[n]	X	X	X	X	X																						

Abbreviations: AE = adverse event; BMI = body mass index; CLDQ = chronic liver disease questionnaire; CTP = Child-Turcotte-Pugh; ECG = electrocardiogram; [redacted]; HCC = hepatocellular carcinoma; IMP = investigational medicinal product; INR = international normalized ratio; IWRS = interactive web response system; MELD = model for end-stage liver disease; PK = pharmacokinetic; TLFB = timeline followback.

a. For patients who roll over from Stage 1 (Phase 2b) into Stage 2 (Phase 3), visits will occur at approximately 78 to 130 weeks after the patient's first dose in the overall study; however, the Case Report Forms will note the infusion visit timepoints as they appear in the Schedule of Assessments.
b. For patients who roll over from Stage 1 (Phase 2b), the Stage 2 (Phase 3) Infusion visit 1 should take place 2 weeks after the last visit in the Phase 2b portion. Also some assessments from the Phase 2b last visit should be considered (and not repeated) for Phase 3 Infusion visit 1 (ie, 12-lead ECG, plasma/serum for storage and gene expression, liver stiffness, liver and abdomen ultrasound, and esophagogastroduodenoscopy).
c. To be administered at the beginning of the visit.
d. Vital sign measurements include heart and respiratory rate, blood pressure, and body temperature prior to IMP administration. Blood pressure will be obtained with the patient in the seated position. Body mass index calculated from body weight and height. Height is measured during Screening Visit 1 only, and that height will be used for all subsequent BMI calculations.
e. Limited physical examination includes examination of the heart, lung, and abdomen.
f. Esophageal hemorrhage, clinically significant ascites requiring hospitalization, overt hepatic encephalopathy, listing for liver transplant, liver transplant, or liver-related death.
g. Urine pregnancy test will be given to females of childbearing potential every 4 weeks during the treatment phase.
h. Hematology will include complete blood cell count (red blood cells, white blood cells, red cell indices, platelets, hemoglobin, and hematocrit) with differential.
i. Blood chemistry will include alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, gamma-glutamyl transferase, and fasting insulin level. Patients must be in a fasted state (at least for 8 hours) prior to blood collection.
j. [redacted].
k. For patients who are newly enrolled in Phase 3.

l. Within 14 to 28 days after the final dose of IMP or where feasible following study termination due to the occurrence of a clinical event or withdrawal of consent. Whenever possible, patients who are terminated from the study, regardless of visit, should also have all the post-study evaluations performed including esophagogastroduodenoscopy and FibroScan.
m. Investigational medicinal product administration will occur after the following procedures: limited physical examination, vital sign measurements, hematology, blood chemistry, biomarker blood samples, and FibroScan.
n. For patients who consent to PK sampling, samples will be collected any time within 1 hour before the first infusion and at 3±1 hours after completing the infusion, 3±1 hours and any time between 24 to 48 hours after completing the second infusion, 3±1 hours and any time 3 to 4 days after completing the third infusion, 3±1 hours and any time 5 to 6 days after completing the fourth infusion, and any time within 1 hour before the fifth infusion and 3±1 hours after completing the infusion. A maximum of 10 samples will be collected per patient. If the 10 plasma samples absolutely cannot occur, the patient should contribute a minimum of 6 PK samples (2 samples per visit) from any of the 3 of the first 5 infusion visits.

Table 7 NAVIGATE Schedule of Assessments –Treatment Phase: Stage 2 (Phase 3) – Weeks 54 to 78[a]

Infusion Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**Early Termination/End of Treatment**	**EOS**
Week ± 3 days	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**14-28 days after the last dose**	**14 days after Early Termination/End of Treatment Visit**
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLDQ[b]														X	X
Alcohol TLFB[b]		X				X				X			X	X	X
Vital sign measurements and BMI[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limited physical examination[d]				X									X	X	X
Assessment of cirrhosis complications[e]				X									X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of dietary and lifestyle recommendation				X									X	X	X
Urine pregnancy test[f]		X		X		X		X		X		X	X	X	X
Urinalysis (dipstick)						X							X	X	X
12-lead ECG													X	X	X
Hematology[g]						X							X	X	X
Blood chemistry[h]						X							X	X	X
Coagulation profile (including INR)						X							X	X	X
Serum sample for [redacted][i]													X	X	
Plasma/serum samples for storage, for future biomarkers and gene expression analysis[i] (optional testing)													X	X	
Liver stiffness assessment (FibroScan)[j]													X	X	
Liver and abdomen ultrasound (for HCC and ascites)													X	X[k]	X
MELD Score						X							X	X	X
CTP Score						X							X	X	X
EGD (upper gastrointestinal endoscopy) with video[l]													X	X[k]	

Infusion Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**Early Termination/End of Treatment**	**EOS**
Week ± 3 days	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**14-28 days after the last dose**	**14 days after Early Termination/End of Treatment Visit**
IMP administration[m]	X	X	X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: AE = adverse event; BMI = body mass index; CLDQ = chronic liver disease questionnaire; CTP = Child-Turcotte-Pugh; ECG = electrocardiogram; EGD = esophagogastroduodenoscopy; [redacted]; EOS = end of study; HCC = hepatocellular carcinoma; IMP = investigational medicinal product; INR = international normalized ratio; IWRS = interactive web response system; MELD = model for end-stage liver disease; TLFB = timeline followback.

a. For patients who roll over from Stage 1 (Phase 2b) into Stage 2 (Phase 3), visits will occur at approximately 132 to 156 weeks after the patient's first dose in the overall study; however, the Case Report Forms will note the infusion visit timepoints as they appear in the Schedule of Assessments.
b. To be administered at the beginning of the visit.
c. Vital sign measurements include heart and respiratory rate, blood pressure, and body temperature prior to IMP administration. Blood pressure will be obtained with the patient in the seated position. Body mass index calculated from body weight and height. Height is measured during Screening Visit 1 only, and that height will be used for all subsequent BMI calculations.
d. Limited physical examination includes examination of the heart, lung, and abdomen.
e. Esophageal hemorrhage, clinically significant ascites requiring hospitalization, overt hepatic encephalopathy, listing for liver transplant, liver transplant, or liver-related death.
f. Urine pregnancy test will be given to females of childbearing potential every 4 weeks during the treatment phase.
g. Hematology will include complete blood cell count (red blood cells, white blood cells, red cell indices, platelets, hemoglobin, and hematocrit) with differential.
h. Blood chemistry will include alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, gamma-glutamyl transferase, and fasting insulin level. Patients must be in a fasted state (at least for 8 hours) prior to blood collection.
i. [redacted]
j. Within 14 to 28 days after the final dose of IMP or where feasible following study termination due to the occurrence of a clinical event or withdrawal of consent. Whenever possible, patients who are terminated from the study, regardless of visit, should also have all the post-study evaluations performed including EGD with video recording documentation and FibroScan.
k. The assessment should not be repeated if previously performed at Infusion Visit 40 (Week 78).
l. Esophagogastroduodenoscopy is to be completed within approximately 2 weeks of the Week 78 visit or study discontinuation regardless of which visit discontinuation occurs. Esophagogastroduodenoscopy must include high resolution videos and will be centrally read.
m. Investigational medicinal product administration will occur after the following procedures: limited physical examination, vital sign measurements, hematology, blood chemistry, biomarker blood samples, EGD with video recording documentation, and FibroScan.

Appendix 6 – Alcohol Use Disorders Identification Test Questionnaire[35]

Box 10

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest.
Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

Appendix 7 – Chronic Liver Disease Questionnaire

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked about your symptoms related to your liver disease, how you have been affected in doing activities, and how your mood has been. Please complete all of the questions and select only **one** response for each question.

1. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

2. How much of the time have you been tired or fatigued during the last 2 weeks?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

3. How much of the time during the last 2 weeks have you experienced bodily pain?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

4. How often during the last 2 weeks have you felt sleepy during the day?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

5. How much of the time during the last 2 weeks have you experienced abdominal pain?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time

6 Hardly any of the time
7 None of the time

6. How much of the time during the last 2 weeks has shortness of breath been a problem for you in your daily activities?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

7. How much of the time during the last 2 weeks have you not been able to eat as much as you would like?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

8. How much of the time in the last 2 weeks have you been bothered by having decreased strength?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

9. How often during last 2 weeks have you had trouble lifting or carrying heavy objects?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

10. How often during the last 2 weeks have you felt anxious?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

11. How often during the last 2 weeks have you felt a decreased level of energy?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

12. How much of the time during the last 2 weeks have you felt unhappy?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

13. How often during the last 2 weeks have you felt drowsy?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

14. How much of the time during the last 2 weeks have you been bothered by a limitation of your diet?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

15. How often during the last 2 weeks have you been irritable?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

16. How much of the time during the last 2 weeks have you had difficulty sleeping at night?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time

5 A little of the time
6 Hardly any of the time
7 None of the time

17. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal discomfort?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

18. How much of the time during the last 2 weeks have you been worried about the impact your liver disease has on your family?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

19. How much of the time during the last 2 weeks have you had mood swings?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

20. How much of the time during the last 2 weeks have you been unable to fall asleep at night?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

21. How often during the last 2 weeks have you had muscle cramps?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

22. How much of the time during the last 2 weeks have you been worried that your symptoms will develop into major problems?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

23. How much of the time during the last 2 weeks have you had a dry mouth?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

24. How much of the time during the last 2 weeks have you felt depressed?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

25. How much of the time during the last 2 weeks have you been worried about your condition getting worse?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

26. How much of the time during the last 2 weeks have you had problems concentrating?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

27. How much of the time have you been troubled by itching during the last 2 weeks?
1 All of the time
2 Most of the time
3 A good bit of the time

4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

28. How much of the time during the last 2 weeks have you been worried about never feeling any better?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

29. How much of the time during the last 2 weeks have you been concerned about the availability of a liver if you need a liver transplant?
1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

Appendix 8 – Alcohol Timeline Followback

A sample timeline followback calendar is provided below. The applicable year and calendar will be used in the actual study. As applicable, units will be calculated using local guidelines and then converted as outlined in the Alcohol Comparison Table (Appendix 9).

Name/ID#: _____ Date: _____

TIMELINE FOLLOWBACK CALENDAR: 2019

1 Standard Drink is Equal to

One 12 oz can/bottle of beer

One 5 oz glass of regular (12%) wine

1 ½ oz of hard liquor (e.g. rum, vodka, whiskey)

1 mixed or straight drink with 1 ½ oz hard liquor

Complete the Following

Start Date (Day 1): _____ End Date (yesterday): _____

MO DY YR MO DY YR

2019	SUN	MON	TUES	WED	THURS	FRI	SAT
			1 New Year's Day	2	3	4	5
J	6	7	8	9	10	11	12
A	13	14	15	16	17	18	19
N	20	21 M. King Day	22	23	24	25	26
	27	28	29	30	31	1	2
F	3	4	5	6	7	8	9
E	10	11	12	13	14 Valentine	15	16
B	17	18 Pres. Day	19	20	21	22	23
	24	25	26	27	28	1	2
M	3	4	5	6	7	8	9
A	10	11	12	13	14	15	16
R	17 St. Patrick	18	19	20	21	22 Good Friday	23
	24 Easter	25	26	27	28	29	30
	31	1	2	3	4	5	6
A	7	8	9	10	11	12	13
P	14	15	16	17	18	19	20
R	21	22	23	24	25	26	27
	28	29	30	1	2	3	4
M	5	6	7	8	9	10	11
A	12 Mother's Day	13	14	15	16	17	18
Y	19	20	21	22	23	24	25
	26	27 Memorial Day	28	29	30	31	

2019	SUN	MON	TUES	WED	THURS	FRI	SAT
							1
J	2	3	4	5	6	7	8
U	9	10	11	12	13	14	15
N	16 Father's Day	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30	1	2	3	4 Independence Dy	5	6
J	7	8	9	10	11	12	13
U	14	15	16	17	18	19	20
L	21	22	23	24	25	26	27
	28	29	30	31	1	2	3
A	4	5	6	7	8	9	10
U	11	12	13	14	15	16	17
G	18	19	20	21	22	23	24
	25	26	27	28	29	30	31
S	1	2 Labor Day	3	4	5	6	7
E	8	9	10	11	12	13	14
P	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30	1	2	3	4	5
O	6	7	8	9	10	11	12
C	13	14 Columbus Day	15	16	17	18	19
T	20	21	22	23	24	25	26
	27	28	29	30	31 Halloween	1	2
N	3	4	5 Election Day	6	7	8	9
O	10	11 Vets. Day	12	13	14	15	16
V	17	18	19	20	21	22	23
	24	25	26	27	28 Thanksgiving	29	30
D	1	2	3	4	5	6	7
E	8	9	10	11	12	13	14
C	15	16	17	18	19	20	21
	22	23	24	25 Christmas	26	27	28
	29	30	31				

Appendix 9 – Alcohol Comparison Table

Alcohol Type	Alcohol by Volume	Volume		Amount of Alcohol	
		Fluid Ounce	mL	Units[a]	Grams
Beer	3.5%	12	350	0.7	9.8
Beer	5%	12	350	1	14
Cider	7%	12	350	1.4	19.6
Distilled spirits or liquor[b]	40%	1.5	45	1	14
Wine	12%	5	150	1	14

[a] Units calculated using the cleave books calculator for units of drink, using the United States definition of 1 unit of alcohol as 17.7 mL (14.0 g) of pure alcohol (http://www.cleavebooks.co.uk/scol/ccalcoh3.htm). Note: As applicable, units will be calculated using local guidelines and then converted as outlined in the Alcohol Comparison Table.

[b] Example, gin, rum, vodka, whiskey

Appendix 10 – Modification of Diet in Renal Disease Calculation

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated creatinine clearance, calculated using the Modification of Diet in Renal Disease algorithm.[36]

This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older. The formula is as follows:

> Glomerular Filtration Rate (mL/min /1.73m^2) = 186 × (serum creatinine [mg/dL])$^{-1.154}$ × (age)$^{-0.203}$ × (1.212, if patient is black) × 0.742 (if female)

Patients with estimated creatinine clearance <45 mL/min calculated by this method will not be allowed to participate in the study.

Appendix 11 – Therapeutic Lifestyle Changes

Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients	
Saturated fats*	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day

* *Trans* fatty acids are another LDL-raising fat that should be kept at a low intake.

Macronutrient Recommendations for the TLC Diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories*
Carbohydrate†	50–60% of total calories*
Dietary fiber	20–30 grams per day
Protein	Approximately 15% of total calories

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.
† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.