CLINICAL STUDY PROTOCOL
IND Number 115459

A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Liver Fibrosis and Resultant Portal Hypertension in Patients with NASH Cirrhosis
The NASH-CX Trial

GT-026

Sponsor:	Galectin Therapeutics Inc 4960 Peachtree Industrial Blvd, Suite 240 Norcross, GA 30071
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Version of Protocol:	GT-026 Original
Date of Protocol:	20 February 2015

CONFIDENTIAL

The study will be conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

Protocol Approval - Sponsor Signatory

Study Title	A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Liver Fibrosis and Resultant Portal Hypertension in Patients with NASH Cirrhosis. The NASH-CX Trial
Protocol Number	GT-026
Protocol Date	20 February 2015

Protocol accepted and approved by:

President, CEO, CMO

Peter G. Traber, MD

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Norcross, GA 30071

Peter G. Traber

Signature

2/20/2015

Date

Protocol Approval - Principal/Coordinating Investigator

Study Title A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Liver Fibrosis and Resultant Portal Hypertension in Patients with NASH Cirrhosis. The NASH-CX Trial

Protocol Number GT-026

Protocol Date 20 February 2015

Protocol accepted and approved by:

Co-Principal Investigator

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2-23-2015
Date

Co-Principal Investigator

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Date

Protocol Approval - Principal/Coordinating Investigator

Study Title A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Liver Fibrosis and Resultant Portal Hypertension in Patients with NASH Cirrhosis. The NASH-CX Trial

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Fort Sam Houston, TX 78234

Signature _____ Date _____

Co-Principal Investigator

Naga Chalasani, MD
Indiana University
Indianapolis, IN 46202

Signature _____ Date 2/23/2015

Declaration of Investigator

I have read and understood all sections of the protocol titled "A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Liver Fibrosis and Resultant Portal Hypertension in Patients with NASH Cirrhosis. The NASH-CX Trial" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1, dated 20 February 2015, the tripartite harmonised International Conference on Harmonisation guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Galectin Therapeutics Inc or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Galectin Therapeutics Inc.

Stephen Harrison
Signature of Principal Investigator

2-23-2015
Date

Stephen A. Harrison
Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	GT-026
Title:	A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Liver Fibrosis and Resultant Portal Hypertension in Patients with NASH Cirrhosis. The NASH-CX Trial
Sponsor:	Galectin Therapeutics Inc 4960 Peachtree Industrial Blvd, Suite 240 Norcross, GA 30071
Study Phase:	Phase 2
Study Centers:	Approximately 45 to 60 study centers in the United States and Canada
Indication:	Portal hypertension with cirrhosis or advanced bridging fibrosis due to nonalcoholic steatohepatitis (NASH)
Rationale:	Nonalcoholic steatohepatitis is a chronic inflammatory disease of the liver characterized by progressive fibrosis that eventually leads to cirrhosis in a subset of subjects; the complications of portal hypertension due to liver fibrosis can result in death or liver transplantation. There are currently no medical therapies approved for NASH or for portal hypertension due to liver fibrosis, and this therapeutic area represents an area of significant unmet medical need. Galectin-3, a protein that binds to galactose-containing oligosaccharides, has been shown to be critical in the pathophysiology of NASH and liver fibrosis. GR-MD-02 galactoarabino-rhamnogalacturnate, a complex carbohydrate drug that binds to galectin-3, has shown robust efficacy in preclinical models of NASH and liver fibrosis and was safe and well tolerated in Phase 1 studies. Therefore, the overall objective of this clinical study is to establish the safety and efficacy of GR-MD-02 as compared to placebo in the reduction of portal pressure as a surrogate for a reduction in fibrosis in subjects with compensated cirrhosis due to NASH.

Objectives:

The primary objective is to evaluate the efficacy of GR-MD-02 on reducing hepatic venous pressure gradient (HVPG) as a measure of portal pressure compared to placebo at 1 year of treatment.

Secondary objectives are to evaluate differences in relevant assessments of fibrosis and cirrhosis between GR-MD-02-treated and placebo-treated subjects. The secondary objectives are to evaluate:

- The effect of GR-MD-02 on change in the collagen proportional area at 1 year compared to placebo as determined by digital morphometric analysis of liver biopsies
- The effect of GR-MD-02 on liver stiffness as determined by FibroScan® score prior to the first infusion, at Infusion Visit 13, and 14-28 days after final infusion as compared to placebo
- The effect of GR-MD-02 on the metabolic capacity of the liver as determined by $cPDR_{30}$ (percentage dose recovery) value of the ^{13}C-methacetin breath test (MBT) (for those study centers where the MBT is available) at screening, at Infusion Visit 13, and 14-28 days after final infusion as compared to placebo
- The effect of GR-MD-02 on progression of cirrhosis at 1 year as compared to placebo, defined as the development of any of the following:
  - esophageal variceal hemorrhage or portal hypertensive gastropathy hemorrhage (confirmed by endoscopy or interventional radiology)
  - clinically apparent ascites
  - spontaneous bacterial peritonitis
  - overt hepatic encephalopathy (defined by the clinical judgment of the principal investigator, but should include the presence of lethargy, disorientation, inappropriate behavior, and the presence of asterixis)
  - an increase in Child-Turcotte-Pugh score ≥2
  - newly diagnosed varices in a subject without prior varices
  - progression from small to medium or large varices

- reaching model for end-stage liver disease score ≥15 as measured on 2 consecutive occasions
- listing for a liver transplant or the performance of a liver transplant
- liver-related mortality

Exploratory objectives are to evaluate:

- Differences in health-related quality of life using the subject-completed chronic liver disease questionnaire following administration of GR-MD-02 or placebo at 1 year.
- Baseline-adjusted change in FibroTest® (FibroSure®) and enhanced liver fibrosis score at Infusion Visits 7, 13, 20, and 14-28 days after final infusion
- Changes in liver biopsy staining for alpha smooth muscle actin and galectin-3 in subjects treated with GR-MD-02 or placebo at 1 year

Safety objectives are to assess the safety and tolerability of GR-MD-02 versus placebo at 1 year.

Pharmacokinetic Objectives are to:

- Evaluate systemic exposure following multiple doses of GR-MD-02 in subjects with portal hypertension due to NASH cirrhosis.
- Explore the population pharmacokinetics of GR-MD-02 in subjects with NASH with portal hypertension and cirrhosis or advanced bridging fibrosis.

Subject Population:

Subjects will be entered into the study and randomly assigned if they have both an HVPG measurement greater than or equal to 6 mm Hg and a liver biopsy with advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6), presumably due to NASH. A liver biopsy diagnosis of cirrhosis or advanced bridging fibrosis, presumably due to NASH will include the following 2 categories: 1) cirrhosis or advanced bridging fibrosis with a definitive pathological diagnosis of NASH (presence of fat, ballooning degeneration, and inflammation) or 2) cirrhosis or advanced bridging fibrosis wherein the subject has greater than 5 years of obesity and/or diabetes with negative viral hepatitis markers and a biopsy showing cirrhosis with any amount of fat.

Additional inclusion criteria will include age at least 18 years and less than or equal to 75 years old at the time of screening, ability to provide written informed consent, and subjects of nonchildbearing potential or willing to use acceptable contraception throughout the duration of the treatment period and for 90 days after their last dose of study treatment.

Exclusion criteria will include current or past history of significant alcohol consumption defined as more than 20 grams per day in females and more than 30 grams per day in males for a period of more than 3 consecutive months within 1 year prior to screening, history of recent weight reduction surgery, presence of a transjugular intrahepatic porto-systemic shunt, history of hepatic decompensation, evidence of other forms of liver disease, laboratory values indicative of advanced cirrhosis (Child-Turcotte-Pugh Class B or C or model for end-stage liver disease greater than or equal to 15), various concomitant illnesses (human immunodeficiency virus-positive subjects, recent major surgery [within 8 weeks of randomization], uncontrolled heart disease, concurrent infection or fever of unknown origin, illicit drug use, history of malignancy), participation in an investigational new drug study within 30 days prior to randomization (including follow-up visits) or at any time during the current study, clinically significant medical or psychiatric condition considered a high risk for participation in a study, failure to give informed consent, and known allergies to the investigational medicinal product (IMP) or any of its excipients.

Study Design:

Study GT-026 is a Phase 2, multicenter, parallel-group, North American, randomized, placebo-controlled, double-blind study. This study will enroll subjects with portal hypertension (HVPG greater than or equal to 6 mm Hg) who also have a liver biopsy showing advanced fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6), presumably due to NASH, excluding subjects with medium and large varices and those with decompensated cirrhosis. All subjects are required to have signed institutional review board- or independent ethics committee-approved informed consent form prior to undergoing any study specific procedures.

Subjects with portal hypertension and advanced bridging fibrosis or cirrhosis will be randomly assigned (1:1:1) to receive 1 of 3 treatment assignments including placebo, GR-MD-02 in a dose of 2 mg/kg lean body mass, or GR-MD-02 in a dose of 8 mg/kg lean body mass administered every other week over a 52-week period for a total of 26 intravenous infusions. The primary endpoint analysis is the baseline-adjusted change in HVPG at 1 year (53-55 weeks) in subjects treated with placebo as compared to subjects treated with GR-MD-02 (2 mg/kg/week or 8 mg/kg/week).

An esophagogastroduodenoscopy (EGD) with evaluation for varices, HVPG, and liver biopsy will be performed before the first infusion and after the final 26th dose of IMP. Additionally, prior to the first infusion, at Infusion Visit 13, and 14 to 28 days following final 26th infusion, subjects will undergo a FibroScan, an MBT (if available), and blood will be collected for assessment of biomarkers.

All subjects are to attend 2 postdose visits: the first will occur 14 to 28 days after the final dose administration and a second will occur 14 days following the first postdose visit.

Subjects will be offered enrollment into a subsequent separate study, an open-label extension study, if there is adequate tolerability and no safety issues or signs of clinical progression that would recommend discontinuation.

Subjects who do not enroll in the open-label extension study will be contacted via telephone every 6 months for 2 years and annually thereafter for a total of 4 years.

Estimated Study Duration:	Subjects will remain on study therapy for a total of 52 weeks unless intolerable side effects develop or the subject is withdrawn from study participation. In addition, subjects will have a 1-week prescreening period, up to an 8-week screening period, and up to a 6-week postdosing period (2 postdose visits) for a total duration of up to 67 weeks.
Efficacy Assessments:	Efficacy assessments will include HVPG measurement, liver biopsy, EGD evaluation, FibroScan, a MBT (if available), progression of cirrhosis, chronic liver disease questionnaire, and serum biomarker tests.
Pharmacokinetic or Pharmacodynamic Assessments:	Plasma levels of GR-MD-02 will be assessed in all subjects. Systemic drug exposure will be assessed at Infusion Visits 1, 2, 3, 4, 7, 10, 13, and 26 during the study. Population pharmacokinetics of GR-MD-02 in subjects with NASH with portal hypertension and cirrhosis or advanced bridging fibrosis will be evaluated.
Safety Assessments:	Safety assessments will include incidence of adverse events (AEs) during study treatment, emergent physical examination abnormalities, emergent vital sign measurements and electrocardiogram abnormalities, and laboratory parameter abnormalities. A data safety monitoring board (DSMB) will be established that includes a panel of at least 3 independent medical experts and an unblinded biostatistician. An official 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. An unblinded monitoring team will also be added to the study. All subjects receiving any part of at least 1 infusion of study treatment will be evaluated for safety. The safety analyses will include evaluation of the incidence of treatment-emergent AEs (TEAEs), grade 3 or greater AEs, serious AEs (SAEs), and TEAEs leading to discontinuation of study treatment using the Common Terminology Criteria for Adverse Events Version 4.0 or higher.

Study Drug, Dosage, and Route of Administration:	Subjects in the GR-MD-02 treatment groups will be randomly assigned to receive either 2 mg/kg lean body weight (up to a maximum of 200 mg total) or 8 mg/kg lean body weight (up to a maximum of 800 mg total). The IMP will be diluted in 100 mL of normal saline and infused intravenously via a peripheral vein over a period of approximately 60 minutes. The IMP will be administered every other week for 52 weeks for a total of 26 doses. No dose modification for GR-MD-02 is allowed. Subjects in the placebo arm will receive placebo diluted in normal saline administered in the same fashion. Active drug and placebo will be blinded (by an unblinded pharmacist) by using amber-colored intravenous bag covers and amber-colored tubing and sealed with tamper-evident tape.
Sample Size:	A total of 52 subjects will be randomly assigned into each of 3 parallel treatment groups in a 1:1:1 ratio for a total of 156 subjects in the study.

Statistical Methods:

All efficacy and safety parameters, subject demographics as well as medical and social history, and other baseline subject characteristics (including prior NASH treatments and associated response/side effects) will be summarized by treatment group for the 3 individual treatment groups, for both GR-MD-02 treatment groups combined versus the placebo group, for the full-analysis (intent-to-treat), modified intent-to-treat, and per-protocol sets.

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

The primary efficacy endpoint analysis will be carried out using an analysis of covariance model, with the HVPG change from baseline at Weeks 53 to 55 as the dependent variable. The model will include treatment group at randomization and the baseline HVPG as a covariate.

Methods for dealing with missing data including dates, efficacy and safety results will be specified in the statistical analysis plan.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 17.1), and summarized by MedDRA system organ class and preferred term. Events from the time of the subject signing informed consent must be reported. Adverse events prior to exposure to IMP are considered pretreatment AEs and will be provided in a listing separate from the listing for TEAEs.

Only TEAEs, and not pretreatment AEs, will be used for tabular summaries and be graded according to the protocol guidelines. Each AE will be assessed for relatedness to the IMP agent per se 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.

All prior treatments for liver cirrhosis and NASH will be recorded in the electronic case report form. All other concomitant medications taken from 30 days prior to screening and throughout the entire duration of the subject's participation in the study will be collected in the electronic case report form. Concomitant medications are defined as medications taken any time after the start of exposure to IMP. Prior medications are defined as nonstudy medications discontinued prior to the start of exposure to IMP. All other concomitant medications taken from 30 days prior to Screening and throughout the entire duration of the subject's time on study will be collected in the electronic case report form. Concomitant medications are defined as medications taken any time after the start of exposure to IMP. Prior medications are defined as medications discontinued prior to the start of exposure to IMP. The prior and concomitant medications taken during the study will be summarized using number of subjects (n) and percentage (%) by individual treatment group, for both GR-MD-02 groups combined, for the placebo group, and overall (all subjects). All prior and concomitant medications will be coded using the WHO Drug Dictionary (Version 1 Sep 2014) and further coded against Anatomic Therapeutic Chemical classification.

Laboratory and vital sign measurement will be evaluated over time using descriptive statistics. Shift analyses of relevant clinical laboratory parameters will be produced showing shifts from baseline across low, normal, and high categories presented by time point.

Date of Protocol: 20 February 2015

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AUDIT	Alcohol Use Disorders Identification Test
BMI	body mass index
CFR	Code of Federal Regulations
CLDQ	chronic liver disease questionnaire
C_{max}	observed maximum plasma or serum concentration after administration
CPA	collagen proportional area
$cPDR_{30}$	percentage dose recovery
CYP3A4	cytochrome P450 3A4
DOB	delta over baseline
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EGD	esophagogastroduodenoscopy
ELF	enhanced liver fibrosis
FAS	full-analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GR-MD-02	galactoarabino-rhamnogalacturnate
HIV	human immunodeficiency virus
HVPG	hepatic venous pressure gradient
ICF	informed consent form
ICH E6(R1)	International Conference on Harmonisation harmonised tripartite guideline
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IWRS	interactive web response system
kPa	kiloPascals

Abbreviation	Definition
LBM	lean body mass
MBT	^{13}C-methacetin breath test
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OLES	open-label extension study
PK	pharmacokinetic
PDR	percentage dose recovery rate
SAE	serious adverse event
SAP	statistical analysis plan
TBW	total body weight
TEAE	treatment-emergent adverse event
TLFB	timeline followback
T_n	time point

1 Introduction

Nonalcoholic fatty liver disease (NAFLD), or fatty liver, and nonalcoholic steatohepatitis (NASH) are common liver disorders in the United States. The major feature in NAFLD is fat accumulation in hepatocytes with minimal inflammation. It is estimated that the worldwide prevalence of NAFLD ranges from 6.3% to 33% with a median of 20% in the general population (Chalasani 2012), but a recent study in asymptomatic middle-aged adults in the US suggests that it may be as high as 46% (Williams 2011). A subset of individuals with NAFLD are found to have NASH, which is characterized by excessive fat accumulation in hepatocytes (steatosis) with the addition of inflammatory cell infiltrates, evidence of damage to hepatocytes (ballooning degeneration), and the deposition of fibrous tissue. It is estimated that 3% to 5% of Americans are affected by NASH (Chalasani 2005), with as many as 12.2% in asymptomatic adults (Williams 2011). While the prevalence of cirrhosis in NASH is not clearly defined, as many as one-third of NASH subjects progress to advanced fibrosis (Caldwell 2010). The only therapy available to these advanced subjects is liver transplantation. Currently the percentage of liver transplantations performed in the US for NASH is between 10% and 15%, but the numbers are increasing and it has been suggested that it may become the leading cause for liver transplantation over the next 20 years (Rinella 2011).

The galectin-3 protein has recently been implicated in the pathogenesis of NASH. Galectins are a family of proteins, containing 15 members (11 identified in humans), which have the property of binding avidly to galactose containing oligosaccharides associated with glycoproteins (Di 2011). GR-MD-02 (galactoarabino- rhamnogalacturnate) represents a new type of agent for the therapy of subjects with NASH and advanced fibrosis. GR-MD-02 is a complex carbohydrate molecule derived from a natural plant compound which contains oligosaccharide chains containing galactose residues and binds to galectin-3, and to a lesser extent, galectin-1. Cellular experiments demonstrate that GR-MD-02 is not toxic to cells but is capable of inhibiting the expression of inflammatory cytokines in a monocyte/macrophage model of inflammation and reduces cell surface galectin-3 from fibrogenic liver stellate cells.

GR-MD-02 has been tested in 2 models of liver fibrosis, a mouse model that reliably produced a pathological picture of NASH with a fibrosis and a toxin-induced model of liver fibrosis in rats. Multiple studies were completed in the mouse NASH model that showed that GR-MD-02 consistently reduced the activity of NASH, reduced or eliminated fibrosis as

measured by liver collagen, and reduced the expression of galectin-3 in liver macrophages (Traber 2013a). Much more robust fibrosis and cirrhosis were induced in rats treated with thioacetamide in which animals developed fibrosis that replaced 25% of the liver with collagen and had all of the pathological characteristics of cirrhosis. Treatment of cirrhotic rats with 4 weekly doses GR-MD-02 resulted in reduction of collagen to below 10%, reversal of cirrhosis, and reduced portal hypertension (Traber 2013b).

The results from a Phase 1 study (Galectin 2014) indicated GR-MD-02 was safe and well tolerated at single and multiple doses of 2, 4, and 8 mg/kg. Pharmacokinetics revealed drug exposure in humans at the 8-mg/kg dose that was equivalent to the upper range of the targeted therapeutic dose determined from effective doses in NASH animal models, thus providing support for the proposed Phase 2 dosing regimen. There was evidence of an effect on a relevant disease marker, with a dose-dependent reduction in FibroTest® (FibroSure®) scores due to a reduction in alpha-2 macroglobulin levels. Additionally, there was a signal of reduced liver stiffness as assessed by FibroScan® in subjects treated with an 8-mg/kg dose of GR-MD-02.

2 Study Objectives

2.1 Primary Objective

The primary objective is to evaluate the efficacy of GR-MD-02 on reducing hepatic venous pressure gradient (HVPG) as a measure of portal pressure compared to placebo at 1 year of treatment.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate differences in relevant assessments of fibrosis and cirrhosis between GR-MD-02-treated and placebo-treated subjects.

The secondary objectives are to evaluate:

- The effect of GR-MD-02 on change in the collagen proportional area (CPA) at 1 year compared to placebo as determined by digital morphometric analysis of liver biopsies
- The effect of GR-MD-02 on liver stiffness as determined by the FibroScan score prior to the first infusion, at Infusion Visit 13, and 14-28 days after final infusion as compared to placebo
- The effect of GR-MD-02 on the metabolic capacity of the liver as determined by $cPDR_{30}$ (percentage dose recovery) value of the ^{13}C-methacetin breath test (MBT) (if available) at screening, at Infusion Visit 13, and 14-28 days after final infusion as compared to placebo
- The effect of GR-MD-02 on progression of cirrhosis at 1 year as compared to placebo, defined as the development of any of the following:
    - esophageal variceal hemorrhage or portal hypertensive gastropathy hemorrhage (confirmed by endoscopy or interventional radiology)
    - clinically apparent ascites
    - spontaneous bacterial peritonitis
    - overt hepatic encephalopathy (defined by the clinical judgment of the principal investigator, but should include the presence of lethargy, disorientation, inappropriate behavior, and the presence of asterixis)
    - an increase in Child-Turcotte-Pugh score ≥2
    - newly diagnosed varices in a subject without prior varices
    - progression from small to medium or large varices
    - reaching a model for end-stage liver disease (MELD) score ≥15 as measured on 2 consecutive occasions
    - listing for a liver transplant or the performance of a liver transplant
    - liver-related mortality

2.3 Exploratory Objectives

The exploratory objectives are to evaluate:

- Difference in health-related quality of life using the subject-completed chronic liver disease questionnaire (CLDQ) following administration of GR-MD-02 or placebo at 1 year
- Baseline-adjusted change in FibroTest (FibroSure) and the enhanced liver fibrosis (ELF) score at Infusion Visits 7, 13, 20, and 14-28 days after final infusion
- Changes in liver biopsy staining for alpha smooth muscle actin and galectin-3 in subjects treated with GR-MD-02 or placebo at 1 year

2.4 Safety Objectives

The safety objectives are to assess the safety and tolerability of GR-MD-02 versus placebo at 1 year.

2.5 Pharmacokinetic Objective

The pharmacokinetic (PK) objectives are to evaluate systemic exposure following multiple doses of GR-MD-02 in subjects with portal hypertension due to NASH cirrhosis and to explore the population pharmacokinetics of GR-MD-02 in subjects with NASH with portal hypertension and cirrhosis or advanced bridging fibrosis.

Note: Formal population PK analysis will not be performed in this study. However, GR-MD-02 plasma levels will be used to evaluate systemic exposure following multiple doses. In the Phase 1 clinical study (Galectin 2014), the observed maximum plasma or serum concentration after administration (C_{max}) drug levels for all doses were well correlated with the area under the concentration-time curve (h*µg/mL) ($p<0.001$, r squared = 0.91). Therefore, C_{max} plasma levels at 2 hours following the dose of GR-MD-02 will be used to estimate the systemic exposure of the drug. Plasma levels of GR-MD-02 will be evaluated at the initiation of the study in all subjects, 2 hours after investigational medicinal product (IMP) infusion at Infusion Visits 1, 2, 3, 4, 7, 10, 13, and 26. Trough levels of drug will not be informative, since there were only measurable levels of drug detected through 72 hours following a dose and were thereafter undetectable (assay limit of detection of 1.2 µg/mL).

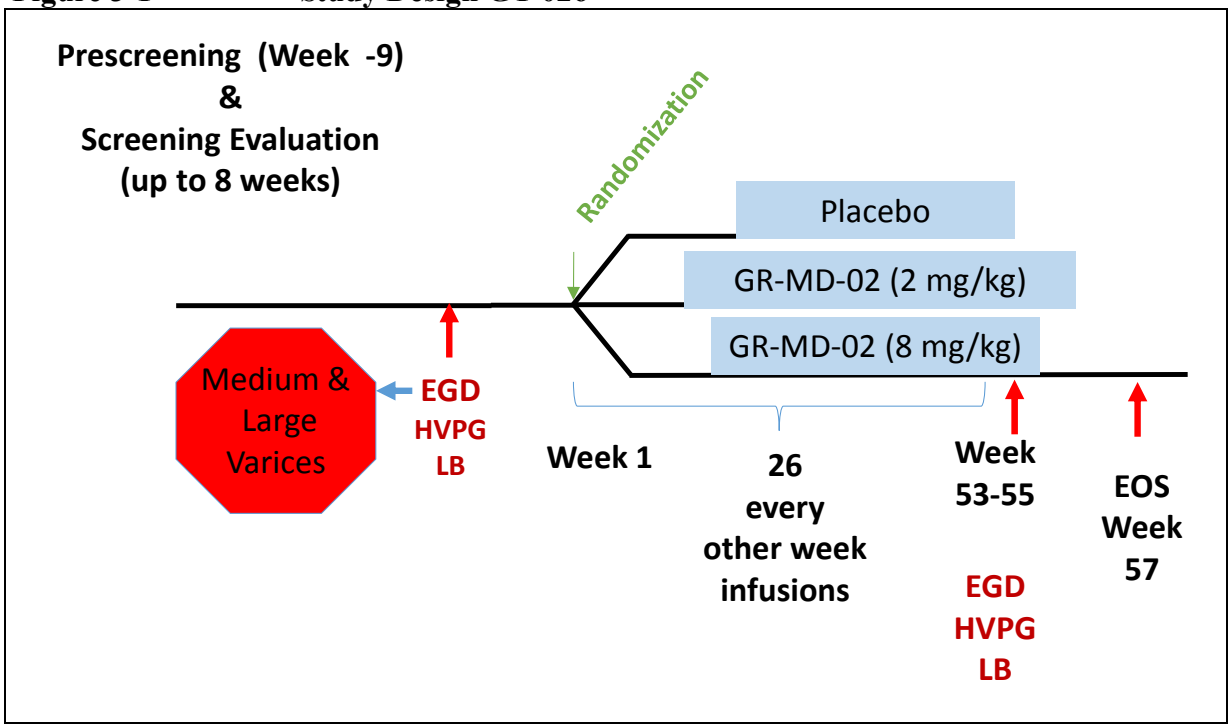
3 Investigational Plan

3.1 Study Design

Study GT-026 is a Phase 2, multicenter, parallel-group, North American, randomized, placebo-controlled, double-blind study of subjects with portal hypertension due to advanced bridging fibrosis or cirrhosis. The study will be conducted in 45 to 60 study centers in the United States and Canada.

This study will enroll subjects with portal hypertension (HVPG greater than or equal to 6 mm Hg) who also have a liver biopsy showing cirrhosis (Ishak stage 5 or 6), or advanced bridging fibrosis (Ishak stage 4) presumably due to NASH, excluding subjects with medium and large varices and those with decompensated cirrhosis (as defined by the presence of clinically detectable ascites, any episode of variceal bleeding, and overt hepatic encephalopathy). Subjects with portal hypertension and the appropriate biopsy findings will be randomly assigned (1:1:1) to receive 1 of 3 treatment assignments: placebo, GR-MD-02 in a dose of 2 mg/kg lean body mass, or GR-MD-02 in a dose of 8 mg/kg lean body mass administered every other week over a 52-week period for a total of 26 infusions (Figure 3-1). The primary endpoint analysis is the baseline-adjusted change in HVPG at 1 year (53 - 55 weeks) in subjects treated with placebo as compared to subjects treated with GR-MD-02 (2 mg/kg/week or 8 mg/kg/week). The model will include treatment group at randomization and the baseline HVPG as a covariate.

Figure 3-1 Study Design GT-026

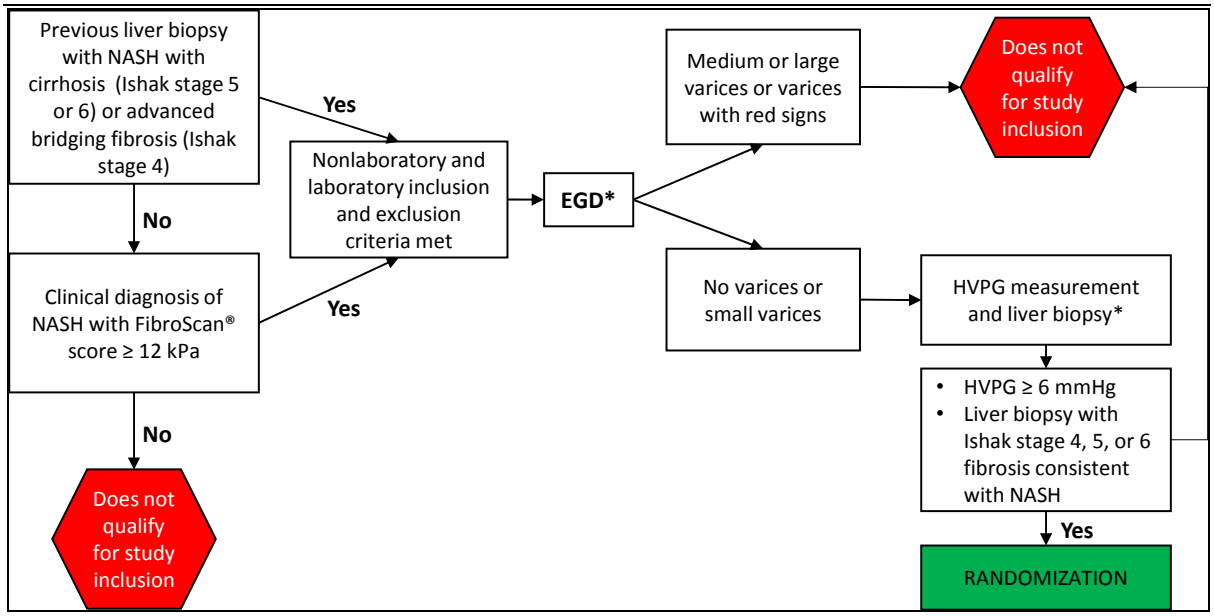


Abbreviations: EGD, esophagogastroduodenoscopy; HVPG, hepatic venous pressure gradient; LB, liver biopsy (percutaneous or transjugular)

The study will include prescreening, screening, randomization, treatment, and follow-up periods. No dose modification for GR-MD-02 will be allowed.

A flow chart depicting the prescreening and screening procedures is provided in Figure 3-2.

Figure 3-2 Prescreening and Screening Flow Chart GT-026



Abbreviations: EGD, esophagogastroduodenoscopy; HVPG, hepatic venous pressure gradient; NASH, nonalcoholic steatohepatitis

Note: ^{13}C-methacetin breath test (if available) to be performed before either EGD, liver biopsy, or HVPG at investigator's discretion.

Prescreening: Prescreening may begin at Week –9. Prior to beginning prescreening procedures, the subject must sign the informed consent form (ICF). Criteria have been established to avoid unnecessary medical procedures (HVPG, esophagogastroduodenoscopy [EGD] and biopsy) in subjects who have a high likelihood of not meeting key study requirements. Subjects who have had a previous liver biopsy with a diagnosis of NASH with either advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6) are eligible to move forward to screening. Subjects with a presumptive clinical diagnosis of NASH (based on the assessment of the principal investigator) will have a FibroScan to assess the potential for fibrosis. Subjects who have a FibroScan score of at least 12.0 kiloPascals (kPa) will be considered to have advanced fibrosis and will proceed to screening. Likewise, subjects with a documented qualifying FibroScan score within the previous 12 months of screening may proceed to screening.

Screening: The screening window is up to 8 weeks.

Subjects will undergo the following required procedures to assess eligibility during the screening period: HVPG measurement, liver biopsy, and EGD. Additionally, at the time of 1 of these 3 procedures (at the discretion of the investigator), subjects will have a MBT performed (if available) prior to the procedure. Eligible subjects will have both an HVPG screening measurement of at least 6 mm Hg and a liver biopsy with advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6), presumably due to NASH. Central reading groups will be used to assess the appropriateness of biopsy and HVPG measurements. A liver biopsy diagnosis of advanced bridging fibrosis or cirrhosis, presumably due to NASH, will include the following 2 categories:

1. Cirrhosis or advanced bridging fibrosis with a definitive pathological diagnosis of NASH (presence of fat, ballooning degeneration, and inflammation) or;

2. Cirrhosis or advanced bridging fibrosis wherein the subject has greater than 5 years of obesity (body mass index [BMI] >30) and/or diabetes with negative viral hepatitis markers and a biopsy showing cirrhosis or advanced bridging fibrosis with any amount of fat

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will proceed to randomization and the treatment phase. Subjects who fail to meet eligibility criteria due to an abnormal laboratory result may undergo retesting of the abnormal laboratory parameter during the screening window and at the discretion of the investigator and with prior approval of the medical monitor.

Treatment Phase: Subjects with portal hypertension who meet all of the other criteria for study inclusion will be randomly assigned (1:1:1) to receive 1 of 3 treatment assignments including placebo, GR-MD-02 in a dose of 2 mg/kg lean body mass, or GR-MD-02 in a dose of 8 mg/kg lean body mass administered every other week over a 52-week period for a total of 26 infusions. During the treatment phase of the study, all subjects randomly assigned to IMP will attend study visits according to the schedule of visits for study administration and monitoring (Table 12-2). Safety (12-lead electrocardiogram [ECG], physical examinations, vital sign measurements, adverse event [AE] monitoring, and safety laboratory assessments), and efficacy (FibroScan, MBT (if available), biomarkers, assessment of cirrhosis complications [esophageal variceal hemorrhage or portal hypertensive gastropathy

hemorrhage, clinically apparent ascites, spontaneous bacterial peritonitis, overt hepatic encephalopathy, listing for a liver transplant or the performance of a liver transplant], and quality of life) will be monitored throughout the treatment phase.

Postdose Final Visit (14-28 days): All subjects will attend a visit (or visits) 14 to 28 days after final dose. During this visit, safety (AE monitoring and safety laboratory assessments) and efficacy (FibroScan, MBT [if available], biomarkers, EGD, HVPG, and a liver biopsy) assessments will be collected/performed (Table 12-2).

Follow-up/Early Termination Visit: All subjects are to attend a follow-up/early termination visit 14 days after the postdose final visit to evaluate safety. During this visit, a 12-lead ECG, a physical examination, vital sign measurements, and AE monitoring will be collected/performed (Table 12-2).

Open-Label Extension Study: Following study completion, subjects will be offered enrollment into a subsequent separate study, an open-label extension study (OLES), if there is adequate tolerability and no safety issues or signs of clinical progression that would require discontinuation.

End-of-Study Telephone Contact: Subjects who do not enroll into the OLES will be contacted via telephone every 6 months for 2 years, and annually thereafter for a total of 4 years, for a brief update and are to be assessed for survival, listing for a liver transplant or the performance of a liver transplant, or complications of chronic liver disease (ascites, spontaneous bacterial peritonitis, variceal bleeding, and encephalopathy; Table 12-3).

3.1.1 Rationale of Study Design

Nonalcoholic steatohepatitis is a chronic inflammatory disease of the liver characterized by progressive fibrosis that eventually leads to cirrhosis in a subset of subjects. Cirrhosis results in portal hypertension, the complications of which (variceal hemorrhage, ascites with bacterial peritonitis, hepatic encephalopathy) can result in death or the need for liver transplantation. There are currently no medical therapies approved for NASH or for portal hypertension by reducing liver fibrosis, and this therapeutic area represents an area of significant unmet medical need. Galectin-3, a protein that binds to galactose-containing oligosaccharides, has been shown to be critical in the pathophysiology of NASH and liver fibrosis. GR-MD-02, a complex carbohydrate drug that binds to galectin-3, has shown robust

efficacy in preclinical models of NASH and liver fibrosis and was safe and well tolerated in Phase 1 studies. Therefore, the overall objective of this clinical study is to establish the safety and efficacy of GR-MD-02 as compared to placebo in the reduction of portal pressure as a surrogate for a reduction in fibrosis in subjects with compensated cirrhosis due to NASH.

Two doses of GR-MD-02 will be evaluated in this clinical study, 2 mg/kg and 8 mg/kg lean body weight. The doses are calculated on lean body weight because the drug is distributed primarily in the blood compartment. These 2 doses were chosen because the drug exposure in humans based on area under the concentration-time curve spans the predicted therapeutic range determined in preclinical studies. The dose of 2 mg/kg is lower than the lowest effective dose evaluated in the preclinical NASH model and 8 mg/kg is in the upper range of the therapeutic window.

GR-MD-02 will be administered every other week over 52 weeks for a total of 26 doses. Liver fibrosis is a chronic condition and, even with an effective therapy, it is likely to require a relatively prolonged therapy to have a clinically relevant effect. Most authorities in the field believe and the US Food and Drug Administration (FDA) advised that 12 months of therapy is likely a minimum required to demonstrate a significant antifibrotic effect.

GR-MD-02 will be compared to a placebo infusion consisting of vials of placebo (phosphate-buffered saline) diluted in 100 mL of normal saline in this study. No therapies have been shown to be effective for the treatment of liver fibrosis in humans and, therefore, placebo is an appropriate comparator.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 156 subjects will be enrolled at 45 to 60 study centers in the United States and Canada. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

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

1. Has a HVPG measurement ≥6 mm Hg.
2. Has a liver biopsy with advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6), presumably due to NASH. A liver biopsy diagnosis of advanced bridging fibrosis or cirrhosis, presumably due to NASH will include the following 2 categories:
    a. Advanced bridging fibrosis or cirrhosis with a definitive pathological diagnosis of NASH (presence of fat, ballooning degeneration, and inflammation) or;
    b. Advanced bridging fibrosis or cirrhosis wherein the subject has greater than 5 years of obesity (BMI >30) and/or diabetes with negative viral hepatitis markers (hepatitis B and hepatitis C) and a biopsy showing any amount of fat.
3. Is ≥18 years of age and ≤75 years of age at the time of screening.
4. Is willing and able to provide written informed consent prior to the initiation of any study-specific procedures.
5. Is not pregnant and must have a negative serum pregnancy test result prior to randomization.

6. If a fertile man or woman participating in heterosexual relations, agrees to use effective means of contraception (ie, 2 effective methods of contraception, one of which must be a physical barrier method).

    - Effective forms of contraception include condom, hormonal methods (birth control pills, injections or implants), diaphragm, cervical cap, or intrauterine device throughout his/her participation in this study and for 90 days after discontinuation of study treatment. 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 vasectomy, hysterectomy, bilateral salpingo-oophorectomy, or bilateral tubal ligation. Postmenopausal women who have been amenorrheic for at least 2 years at the time of screening will be considered sterile.

7. 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.
8. 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 subjects 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.
9. Prior to randomization, any subject on statins, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or β-1 selective adrenergic receptor inhibitors should have been on a stable dose for at least 2 months and all attempts should be made to continue the subject on the same dose of the medication for the duration of study participation.

4.1.2 Exclusion Criteria

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

1. Has a history of hepatic decompensation including any episode of variceal bleeding, clinically detectable ascites, or overt hepatic encephalopathy (defined by the clinical judgment of the principal investigator but should include the presence of lethargy, disorientation, inappropriate behavior, and the presence of asterixis).

2. Has a presence of medium or large varices or varices with red signs regardless of size based on endoscopy.

    - Small varices are defined by veins that occupy >25% of the distal one third of the esophageal lumen when insufflated. Veins that completely flatten upon insufflation of the esophagus are not conserved varices. Any varices larger than that are medium (up to 50%) or large (>50%).

    - Red signs include red wale markings (dilated venules oriented longitudinally on the variceal surface), cherry red spots (small, red, spotty dilated venules usually approximately 2 mm in diameter on the variceal surface) or hematocystic spots (large, round, crimson red projection >3 mm that look like a blood blister on the variceal surface).

3. Has had a prior transjugular porto-systemic shunt procedure.

4. Has evidence of other forms of chronic liver disease including viral hepatitis B or C, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alpha-1 antitrypsin deficiency, alcoholic hepatitis, hemochromatosis, liver cancer, history of biliary diversion, or autoimmune hepatitis.

5. Has any of the following laboratory values:

    a. Serum alanine aminotransferase levels >10 × the upper limits of normal

    b. Serum aspartate aminotransferase levels >10 × the upper limits of normal

    c. Serum creatinine ≥2.0 mg/dL

    d. Platelet count <60 000/mm^3

    e. Serum albumin ≤2.8 g/dL

    f. International normalized ratio (INR) ≥1.7

    g. Direct bilirubin ≥2.0 mg/dL

6. A MELD score ≥15 or Child-Turcotte-Pugh Class B or C.

7. Is unwilling or unable to safely undergo HVPG or liver biopsy.

8. Has known positivity for human immunodeficiency virus (HIV) infection or a positive HIV test result at screening.

9. Has had major surgery within 8 weeks of randomization, significant traumatic injury within 6 months, or anticipation of need for major surgical procedure during the course of the study.

10. Has a history of a solid organ transplant requiring current immunosuppression therapy.

11. Has used nonselective β-adrenergic inhibitors within 6 weeks prior to randomization or at any time during the study.

12. Has planned or anticipated variceal ligation therapy during the study.

13. Has had weight reduction surgery within the past 3 years or plans to undergo weight reduction surgery during the study.

14. Has current, significant alcohol consumption or a history of significant alcohol consumption for a period of more than 3 consecutive months any time within 1 year prior to screening.

    - 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 United States is considered to be 14 g of alcohol equivalent to 12 fluid oz of regular beer (5% alcohol), 5 fluid oz of table wine (12% alcohol), or 1.5 fluid oz of 80 proof spirits (40% alcohol).
      A score of ≥8 on the Alcohol Use Disorders Identification Test (AUDIT) (Babor 2000) will result in exclusion. (The AUDIT is provided in Section 12.2.)

15. Has a positive urine screen result for amphetamines, cocaine, or nonprescription opiates (heroin, morphine) at screening.

16. Has clinically significant and uncontrolled cardiovascular disease (eg, uncontrolled hypertension, myocardial infarction within 6 months prior to randomization, unstable angina), New York Heart Association Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring devise/ablation or Grade II or greater peripheral vascular disease within 12 months prior to randomization.

17. 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 subject a poor candidate for inclusion into the study.

18. Has concurrent infection including diagnoses of fever of unknown origin at the time of randomization (subjects must be afebrile at the start of therapy).

19. Has a history of malignancy, except for the following adequately treated nonmetastatic basal cell skin cancer; any other type of skin cancer, except melanoma, that has been adequately treated and has not recurred for at least 1 year prior to enrollment; and adequately treated in situ cervical cancer that has not recurred for at least 1 year prior to screening.

20. Participates in an investigational new drug study within 30 days prior to randomization (including follow-up visits) or at any time during the current study.

21. Has a clinically significant medical or psychiatric condition considered high risk for participation in an investigational study.

22. Fails to give informed consent.

23. Has known allergies to the IMP or any of its excipients.

24. Is an employee or family member of the investigator or study center personnel.

25. Needs concomitant use of drugs with a narrow therapeutic window metabolized by cytochrome P450 3A4 (CYP3A4) isozyme including specifically the fast-acting opioids alfentanil and fentanyl; the immunosuppressive drugs cyclosporine, sirolimus, and tacrolimus; the cardiovascular agents ergotamine, quinidine, and dihydroergotamine; and the psychotropic agent pimozide.

4.2 Withdrawal of Subjects from the Study

The duration of the study is defined for each subject as the date a signed written informed consent is provided through the last follow-up visit, up to 42 days following the last IMP infusion.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects 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 keep subjects in the study. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. Significant noncompliance with the protocol
2. A serious or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study
3. Laboratory safety assessments that reveal clinically significant hematological or biochemical changes from the baseline values
4. Symptoms or an intercurrent illness not consistent with the protocol requirements for study participation or that justifies withdrawal
5. Lost to follow-up
6. Pregnancy
7. The subject withdraws consent or the investigator or sponsor decides to discontinue the subject's participation in the study.

The investigator will also withdraw subjects if Galectin Therapeutics Inc terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved. Any subject may withdraw his or her consent at any time.

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Subjects who discontinue study treatment or active participation in the study will no longer receive IMP. When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all subjects who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-study assessments. Subjects who fail to return for final assessments will be contacted by the study center (2 documented telephone calls followed by 1 registered letter) in an attempt to have them comply with the protocol.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

4.2.3 Replacements

Subjects who are randomly assigned to IMP and prematurely discontinued from the study will not be replaced.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to receive 2 mg/kg lean body weight of GR-MD-02, 8 mg/kg lean body weight of GR-MD-02, or placebo using a 1:1:1 allocation ratio. An interactive web response system (IWRS) will be used to administer the randomization schedule. Unblinded biostatistics personnel not participating in the conduct of the study will generate the randomization schedule using SAS software Version 9.2 or later (SAS Institute Inc, Cary, North Carolina) for IWRS, which will link sequential subject randomization numbers to treatment codes.

The IWRS will send visit notifications to the study center personnel confirming the subject data that were entered. All study visits will have a visit window of ± 3 days. The IWRS notifications should be filed in source.

5.2 Treatments Administered

The GR-MD-02 for injection is supplied in a sterile aqueous solution of phosphate-buffered saline at a concentration of 30 mg/mL GR-MD-02 and should be diluted to the target dose in normal saline and administered intravenously over a period of approximately 60 minutes. The product is expected to be stable at pH 4.0 to 7.5.

GR-MD-02 solution will be supplied in 10-mL vials with the following composition to the study center (Table 5-1).

Table 5-1 Composition of GR-MD-02 Concentrate

Ingredient	Concentration
GR-MD-02	300 mg
USP sodium chloride	82 mg
USP disodium phosphate heptahydrate	14.4 mg
USP monosodium phosphate monohydrate	2.4 mg
USP sterile water for injection	to 10 mL

Instructions on dosing preparation are provided in the Pharmacy Manual.

Once the infusion solutions are prepared, they may be stored at a room temperature (20°C-25°C [68°F-77°F]) and should be administered within 24 hours of preparation. Infusions should be administered intravenously over a period of approximately 60 minutes. Frequency of administration should be once every 2 weeks (Table 12-2).

5.3 Identity of Investigational Medicinal Product

GR-MD-02 (galactoarabino-rhamnogalacturnate) is a soluble polysaccharide composed of an alternating α-(1,2)-L-rhamnosyl-α-(1,4)-D-galacturonosyl backbone with side branches composed of mainly galactose and arabinose oligosaccharides.

GR-MD-02 for injection is a clear, light yellow-tan solution and is supplied in 10-mL sterile vials at a concentration of 30 mg/mL of GR-MD-02 in phosphate-buffered saline.

Detailed instructions for the preparation and administration of the GR-MD-02 by slow intravenous (IV) drip over a period of approximately 60 minutes will be provided in the Pharmacy Manual.

Lean body mass (LBM) will be used for dosing because it is anticipated that many subjects will be obese and GR-MD-02 is distributed primarily in the blood compartment. Lean body mass will be estimated from height and weight measurements using formulas that have been well-validated in obese individuals (Janmahasatian 2005):

- Males: LBM = 9270 × TBW (total body weight)/(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). 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.

The study pharmacist at each study center will be unblinded in the preparation of IMP for infusion. Infusion solutions will be prepared as specified in the Pharmacy Manual in IV bags and placed in amber-colored IV bag covers with amber-colored tubing and infusion sets. The amber-colored bags will be sealed with tamper-evident tapes. Once prepared by the unblinded pharmacist, the placebo and drug solutions in the IV infusion set-up will be indistinguishable. Thus, the study subjects, primary investigators, and medical personnel will

be blinded throughout the study as to whether the subject is receiving active drug or placebo. Upon completion of IMP infusion, documentation of the discarded infusion set must be recorded to indicate no unblinding occurred.

5.4 Management of Clinical Supplies

5.4.1 Investigational Medicinal Product Packaging and Storage

Galectin Therapeutics Inc will provide IMP to the study centers. The following drug supplies will be used in the study:

- GR-MD-02, supplied as 10-mL sterile vials
- Placebo (phosphate-buffered saline solution), supplied as 10-mL sterile vials

GR-MD-02 for injection (30 mg/mL) and placebo to be used for the study (phosphate-buffered saline) in 10-mL vials are manufactured by Catalent Pharma Solutions, Woodstock, Illinois, and packaged and labeled for the study center by Catalent Pharma Solutions, Philadelphia, Pennsylvania.

The GR-MD-02 for injection (30 mg/mL) vials and placebo vials are to be stored under refrigerated conditions at 2°C to 8°C (36°F-46°F) until preparation of the drug infusion solution. To prepare the final infusion solution for administration, the GR-MD-02 will be diluted in sterile normal saline as required to achieve the target dose. Instructions on dosing preparation are provided in the Pharmacy Manual.

5.4.2 Test Article Accountability

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 subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. Upon completion of IMP infusion, documentation of the discarded infusion set must be recorded to indicate no unblinding occurred. 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.

5.4.3 Other Supplies

In addition to drug and placebo for the study, each study center will also be provided sterile syringe filters, amber-colored bag covers (with tamper-evident tape) and amber-colored infusion tubing sets. See the Pharmacy Manual for the specifications and details regarding these ancillary supplies.

5.5 Overdose Management

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to PPD Pharmacovigilance:

- **SAE Hotline: 1-800-201-8725**
- **SAE Fax line: 1-888-488-9697**

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.

5.5.1 Treatment of Overdose

There are no known or anticipated adverse effects of GR-MD-02 overdose. The subject should be observed, but there are no specific therapies to be instituted.

5.5.2 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.

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

Any AEs resulting from medication errors will be recorded as AEs in the eCRF.

5.5.3 Treatment of Medication Errors

Should a medication error occur, the subject should be observed; however, there are no specific therapies to be instituted.

5.6 Misuse for Illegal Purposes

GR-MD-02 does not have known effects that may be addictive and there are no other known reasons for misuse.

5.7 Blinding

The aqueous solution of GR-MD-02 is light yellow-tan. It has not been possible to match the color with a placebo formulation. Therefore, the study pharmacist at each study center will be unblinded in the preparation of IMP for infusion. The formulated 10-mL solutions will be prepared for infusion as specified in the Pharmacy Manual in IV bags and placed in amber-colored IV bag covers with amber-colored tubing and infusion sets. The amber-colored bags will be sealed with tamper-evident tape. Placebo and drug solutions to be administered in the IV infusion set up are indistinguishable. Thus, the study subjects, primary investigators, and medical personnel will be blinded to the identity of the administration. Infusion of the IMP causes no local reaction in animal studies or in humans participating in the Phase 1 clinical study and, therefore, should not affect blinding.

5.7.1 Breaking the Blind

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject depends on knowing the study treatment the subject received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation. 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 subject. 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.

5.8 Treatment Compliance

Subject compliance will be determined by infusion records.

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

5.9 Prior and Concomitant Therapy

Use of all concomitant medications will be recorded in the subject's eCRF. The minimum requirement is that drug name, reason for use, dose, and the dates of administration will be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the subject's eCRF.

All prior treatments for liver cirrhosis and NASH will be recorded in the eCRF. All other concomitant medications taken from 30 days prior to screening and throughout the entire duration of the subject'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 nonstudy medications discontinued prior to the start of exposure to IMP.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If prohibited medications are needed for the welfare of the subject, the subject should be discontinued from the study. It is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

5.10 Prohibited Medications or Therapies

Excluded from use are drugs with a narrow therapeutic window metabolized by CYP3A4, including specifically the fast-acting opioids alfentanil and fentanyl; the immunosuppressive drugs cyclosporine, sirolimus, and tacrolimus; the cardiovascular agents ergotamine, quinidine, and dihydroergotamine; and the psychotropic agent pimozide. In vitro experiments

have shown some inhibition of CYP3A4 enzyme expression and activity at levels of drug exposure much higher than obtained in this study. A human drug-drug interaction study is being conducted to evaluate whether there are any changes in in the pharmacokinetics of a model CYP3A4-metabolized drug. Once the results of this study are available, this exclusion criterion may be modified.

Nonselective β-adrenergic inhibitors for the purpose of treatment of portal hypertension are prohibited during the study as well as any off-label drugs.

6 Study Assessments and Procedures

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Manual/Investigator Site File Notebook which will provide the study center personnel with administrative and detailed technical information that does not impact subject safety.

Before any study procedures are performed, all potential subjects will sign an ICF. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator will also sign the ICF.

The schedule of events for prescreening and screening is provided in Table 12-1, for randomization, treatment phase, and follow-up in Table 12-2, and for the end-of-study telephone contact in Table 12-3.

6.1 Study Visits

6.1.1 Prescreening Visit (Week –9)

After the subject has provided informed consent, the following information will be collected (Table 12-1):

- Enter the IWRS and register subject visit data.
- NASH diagnosis: Subjects who have had a previous liver biopsy with a diagnosis of NASH with either advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6) are eligible to move forward to screening.
- Conduct a FibroScan: Subjects with a presumptive clinical diagnosis of NASH (based on the assessment of the principal investigator) will have a FibroScan to assess the potential of fibrosis. Subjects who have a FibroScan score of ≥12.0 kPa will be considered to have advanced fibrosis and will proceed to screening. Likewise, subjects with a documented qualifying FibroScan score within the previous 12 months of screening may proceed to screening.

6.1.2 Screening Visit (Week -8 to Day 0)

The screening visit window is up to 8 weeks after the prescreening visit. Subjects who fail to meet eligibility criteria within this 8-week period due to an abnormal laboratory result may undergo retesting of the abnormal laboratory parameter during the screening window and at the discretion of the investigator and with prior approval of the medical monitor. During the screening visit, the following information will be collected (Figure 3-2 and Table 12-1):

- Enter the IWRS and register subject visit data.
- Inclusion/exclusion criteria include AUDIT alcohol consumption questionnaire. The AUDIT is a screening tool to identify the early signs of hazardous and harmful drinking and identify mild dependence. This questionnaire (10 questions total) will be given to the subject at the beginning of the screening visit and will be considered source documentation. The subject will sign and date the questionnaire upon completion.
- Collect demographic information.
- Collect medical, surgical, and medication history (concomitant medications taken from 30 days prior to screening).
- Perform a 12-lead ECG assessment.
- Perform hematology testing.
- Perform blood chemistry testing.
- Perform coagulation profile.
- Obtain MELD score.
- Perform viral hepatitis B and C serology.
- Perform HIV serology.

- Perform urine drug screen for amphetamines, cocaine, and nonprescription opiates.
- Perform urinalysis testing.
- Perform serum pregnancy test (females of childbearing potential only).
- Perform chest radiograph (posterior-anterior and lateral views).
- Obtain Child-Turcotte-Pugh score and class (A, B, or C).
- Perform a complete physical examination (including height [in centimeters] and weight [in kilograms]) with particular attention to examination for stigmata of liver disease/cirrhosis.
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform MBT (if available) prior to EGD, HVPG, or liver biopsy (at the discretion of the investigator).
- EGD
  Subjects will have had an EGD within 2 months prior to randomization. Subjects with medium or large varices or varices with red signs (red wale marks or red spots), regardless of size, will be excluded from study participation. Subjects without varices or with small varices will continue to HVPG measurement and liver biopsy.
- Obtain demographic information.
- HVPG
  Subjects must have both an HVPG measurement ≥6 mm Hg and a liver biopsy with advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6), presumably due to NASH. Subjects without varices or with small varices will have hepatic venous catheterization with measurement of both wedged and free hepatic venous pressures and standardized calculation of the HVPG prior to randomization and first IMP infusion.

- Obtain liver biopsy
  Liver biopsy may be obtained via a percutaneous approach or a transjugular approach during the HVPG procedure, at the preference of the investigator.

- AE monitoring.

6.1.3 Treatment Phase

6.1.3.1 Randomization

Randomization must occur between 3 and 8 weeks after screening has begun. The IWRS will be used to administer the randomization schedule.

Prior to Infusion Visit 1, subjects with portal hypertension and the appropriate biopsy will be randomly assigned (1:1:1) to receive 1 of 3 treatment assignments: placebo, GR-MD-02 in dose of 2 mg/kg lean body mass, or GR-MD-02 in a dose of 8 mg/kg lean body mass. Subjects will be entered into the study and randomly assigned if they have both an HVPG screening measurement greater than or equal to 6 mm Hg and a liver biopsy with advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6), presumably due to NASH and meet all inclusion criteria and no exclusion criteria.

6.1.3.2 Two Weeks Prior to Infusion Visit 1

Within 2 weeks prior to the first infusion, a FibroScan will be conducted.

6.1.3.3 Infusion Visit 1 (Week 1)

During the Infusion 1 Visit, the following procedures and assessments will be performed after randomization and prior to administration of IMP (Table 12-2):

- Enter the IWRS and register subject visit data.

- CLDQ (This questionnaire will be given to the subject at the beginning of the visit and will be considered source documentation.)

- Alcohol timeline followback (TLFB) (This will be given to the subject at the beginning of the visit and will be considered source documentation.)

- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen).
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform hematology testing.
- Perform blood chemistry testing.
- Collect biomarkers blood sample (will include the ELF test and FibroTest [FibroSure], and galectin-3).
- Collect plasma and serum sample for storage at –20°C.

The following information will be collected after IMP administration:

- AE monitoring.
- Record concomitant medications.

The following will be performed 2 hours after the end of the IMP infusion:

- Collect PK sample.

6.1.3.4 Infusion Visits 2, 3, 4, 5, and 6 (Weeks 3, 5, 7, 9, and 11 ± 3 Days, respectively)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data.
- Alcohol TLFB (This will be given to the subject at the beginning of the visit and will be considered source documentation.) (Infusion Visit 5)
- Assessment of cirrhosis complications (Infusion Visits 3 and 5).
- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen).

- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform urine pregnancy test (females of childbearing potential only) (Infusion Visits 3 and 5).

The following information will be collected after IMP administration:

- AE monitoring.
- Record concomitant medications.

The following will be performed 2 hours after the end of the IMP infusion

- Collect PK sample (Infusion Visits 2, 3, and 4)

6.1.3.5 Infusion Visit 7 (Week 13 ± 3 Days)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data
- Assessment of cirrhosis complications
- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen)
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature)
- Perform urine pregnancy test (females of childbearing potential only)
- Perform hematology testing
- Perform blood chemistry testing

The following information will be collected after IMP administration:

- AE monitoring

- Record concomitant medications

The following will be performed 2 hours after the end of the IMP infusion

- Collect PK sample

6.1.3.6 Infusion Visits 8, 9, 10, 11, and 12 (Weeks 15, 17, 19, 21, and 23 ± 3 Days)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data.
- Assessment of cirrhosis complications (Infusion Visits 9 and 11).
- Alcohol TLFB (This will be given to the subject at the beginning of the visit and will be considered source documentation.) (Infusion Visit 9)
- Perform a limited physical examination including weight and examination of the heart, lung, and abdomen).
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform urine pregnancy test (females of childbearing potential only) (Infusion Visits 9 and 11).

The following information will be collected after IMP administration:

- AE monitoring.
- Record concomitant medications.

The following will be collected 2 hours after IMP infusion

- Collect PK sample (Infusion Visit 10).

6.1.3.7 Infusion Visit 13 (Week 25 ± 3 Days)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data.
- Alcohol TLFB (This questionnaire will be given to the subject at the beginning of the visit and will be considered source documentation.)
- Assessment of cirrhosis complications.
- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen).
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform urine pregnancy test (females of childbearing potential only).
- Perform hematology testing.
- Perform blood chemistry testing.
- Obtain MELD score.
- Conduct a FibroScan.
- Perform MBT (if available).
- Collect biomarkers blood sample (will include the ELF test, FibroTest [FibroSure], and galectin-3).
- Collect plasma and serum sample for storage at –20°C.

The following information will be collected after IMP administration:

- Perform a 12-lead ECG assessment.
- Obtain Child-Turcotte-Pugh score and class (A, B, or C).
- AE monitoring.
- Record concomitant medications.

The following will be collected 2 hours after the end of the IMP infusion

- Collect PK sample

6.1.3.8 Infusion Visits 14, 15, 16, 17, 18, and 19 (Weeks 27, 29, 31, 33, 35, and 37 ± 3 Days)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data.
- Alcohol TLFB (This questionnaire will be given to the subject at the beginning of the visit and will be considered source documentation.) (Infusion Visit 17)
- Assessment of cirrhosis complications (Infusion Visits 15, 17, and 19).
- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen).
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform urine pregnancy test (females of childbearing potential only) (Infusion Visits 15, 17, and 19).

The following information will be collected after IMP administration:

- AE monitoring.
- Record concomitant medications.

6.1.3.9 Infusion Visit 20 (Week 39 ± 3 Days)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data
- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen)

- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature)
- Perform hematology testing
- Perform blood chemistry testing

The following information will be collected after IMP administration:

- AE monitoring
- Record concomitant medications

6.1.3.10 Infusion Visit 21 (Week 41 ± 3 Days)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data.
- Alcohol TLFB (This questionnaire will be given to the subject at the beginning of the visit and will be considered source documentation.)
- Assessment of cirrhosis complications.
- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen).
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform urine pregnancy test (females of childbearing potential only).

The following information will be collected after IMP administration:

- AE monitoring.
- Record concomitant medications.

6.1.3.11 Infusion Visits 22, 23, 24, and 25 (Weeks 43, 45, 47, and 49 ± 3 Days)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data.
- Alcohol TLFB (This questionnaire will be given to the subject at the beginning of the visit and will be considered source documentation.) (Infusion Visit 25)
- Assessment of cirrhosis complications (Infusion Visits 23 and 25).
- Perform a limited physical examination including weight and examination of the heart, lung, and abdomen).
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform urine pregnancy test (females of childbearing potential only) (Infusion Visits 23 and 25).

The following information will be collected after IMP administration:

- AE monitoring.
- Record concomitant medications.

6.1.3.12 Infusion Visit 26 (Week 51 ± 3 Days)

The following procedures and assessments will be performed prior to administration of IMP:

- Enter the IWRS and register subject visit data.
- CLDQ (This questionnaire will be given to the subject at the beginning of the visit and will be considered source documentation.)
- Assessment of cirrhosis complications.

- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen).
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature).
- Perform hematology testing.
- Perform blood chemistry testing.
- Obtain MELD score.
- Collect plasma and serum sample for freezing at –20°C.

The following information will be collected after IMP administration:

- Obtain Child-Turcotte-Pugh score and class (A, B, or C).
- AE monitoring.
- Record concomitant medications.

The following will be collected 2 hours after the end of the IMP infusion:

- Collect PK sample

6.1.4 Follow-up (14-28 Days After Final Dose; Weeks 53-55 ± 3 Days)

Within 14 to 28 days after the final 26th dose of IMP or, where feasible, following study termination, the following information will be collected (Table 12-2):

- Enter the IWRS and register subject visit data
- Perform a limited physical examination including weight and examination of the heart, lung, and abdomen)
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature)

- Conduct a FibroScan
- Perform MBT (if available)
- Collect biomarkers blood sample (will include the ELF test, FibroTest [FibroSure], and galectin-3)
- Perform EGD (must be performed on a different day within the 14 to 28-day follow-up period than when the HVPG assessment is performed)
- Perform HVPG
- Obtain a liver biopsy
- Perform hematology testing
- Perform blood chemistry testing
- AE monitoring
- Record concomitant medications

6.1.5 Follow-up/Early Termination (Week 57 ± 3 Days)

Fourteen days after the previous visit (Section 6.1.4), the following information will be collected (Table 12-2):

- Enter the IWRS and register subject visit data
- Perform a 12-lead ECG assessment
- Perform a limited physical examination (including weight and examination of the heart, lung, and abdomen)
- Collect vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature)
- AE monitoring

- Record concomitant medications

6.1.5.1 Open-Label Safety Extension Study

Following study completion, subjects will be offered enrollment into a subsequent separate study, an OLES if there is adequate tolerability and no safety issues or signs of clinical progression that would recommend discontinuation.

6.1.6 End-of-Study Telephone Contact

Subjects who do not enroll in the OLES will be contacted via telephone every 6 months for 2 years, and annually thereafter for a total of 4 years, for a brief update. Subjects are to be assessed for survival, listing for a liver transplant or the performance of a liver transplant, or complications of chronic liver disease (ascites, spontaneous bacterial peritonitis, variceal bleeding, and encephalopathy; Table 12-3).

6.2 Efficacy Assessments

Refer to the Study Manual for specific procedures to be followed for the various efficacy assessments. Timing of the efficacy assessments is provided in the schedule of events in Table 12-2, and Table 12-3.

6.2.1 HVPG Measurement

Evaluation of portal hypertension will be done using HVPG measurement. Subjects without varices or with small varices will have hepatic venous catheterization with measurement of both wedged and free hepatic venous pressures and standardized calculation of the HVPG prior to randomization and first IMP dose. All HVPG pressure tracings will be performed according to the study guidelines provided in the Study Manual. All HVPG tracings will be evaluated at a central reading facility by a single experienced investigator (Dr Guadalupe Garcia-Tsao, Yale University) to confirm that the subjects meet criteria for inclusion prior to randomization.

Blinded paired HVPG tracings from prior to randomization and at the end of the study will be evaluated at the same central facility by the experienced investigator.

6.2.2 Liver Biopsy

Liver biopsies will be evaluated to determine the general pathological diagnosis and to quantitatively evaluate the degree of liver fibrosis. In a central pathology laboratory, paired biopsies from baseline and the end of treatment for each individual will be stained with Sirius red, which stains specifically type I collagen, and digital morphometry used to quantitate the percentage of the liver biopsy that stains with Sirius red, as previously described (McHutchison 2010). The change in liver collagen (a surrogate for fibrosis) will be measured by the change in the CPA at 1 year on paired liver biopsies from prior to randomization and at the end of study. All liver biopsies will be performed according to the study guidelines provided in the Study Manual. Liver biopsies will be evaluated at a central pathology laboratory by a single, experienced pathologist (Dr. Zack Goodman, INNOVA Medical Center).

In addition, as exploratory endpoints, liver biopsies will be stained with antibodies to alpha smooth muscle and galectin-3 and similarly quantified (McHutchison 2010). The change in staining of these 2 proteins will be compared for each subject at baseline and the end of treatment.

6.2.3 FibroScan

FibroScan is an FDA approved, noninvasive 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 of kPa. The stiffness of the liver correlates with the degree of liver fibrosis as assessed by liver biopsy, including subjects with NASH (Wong 2010). One advantage of this method is that the volume of liver tissue assessed is approximately 100 times greater than volume assessed by liver biopsy. As such, FibroScan represents a promising noninvasive, outpatient method for measuring changes in liver fibrosis over time. FibroScan evaluations will be performed after an 8-hour fast according to the study guidelines provided in the Study Manual and as per the manufacturer's instructions.

6.2.4 ^{13}C-methacetin Breath Test

The MBT is a noninvasive tool to assess microsomal capacity to metabolize the nonradioactive ^{13}C-labeled methacetin. For those study centers where the MBT is approved,

the test will be performed after an 8-hour fast according to the study guidelines provided in the Study Manual and as per the manufacturer's instructions. The study center will make a follow-up telephone call to the subject to capture any AEs that may have occurred within 48 hours after the breath test.

The Breath Test System consists of the BreathID® MCS device and a test kit containing a breath collection cannula and a nonradioactive isotope ^{13}C-methacetin solution. The BreathID device measures and computes the $^{13}CO_2/^{12}CO_2$ ratio in the subject's exhaled breath in real time.

The device is based on an FDA-approved device (510k#: K130524) for assessment of *Helicobacter pylori* infection in the stomach utilizing ^{13}C-urea as a substrate. Performance and safety of the device utilizing the ^{13}C-methacetin substrate for assessment of liver function have been studied in thousands of subjects worldwide, including in a large US pivotal study (G080107) enrolling over 400 subjects with chronic liver disease from 11 participating sites (including 141 subjects with biopsy proven cirrhosis). This study demonstrated an excellent safety profile of the MBT. Furthermore, there are currently 2 ongoing studies (G140190, G140254) for detection of clinically significant portal hypertension in subjects with advanced liver disease and for assessment of correlation to severity of liver disease in subjects with NAFLD.

The MBT parameter to be used in the current study is the $cPDR_{30}$, which is the cumulative percentage dose recovery of the metabolized ^{13}C-methacetin 30 minutes after ingestion of the test substrate. It is obtained by using the following steps:

1. All delta over baseline (DOB) measures with corresponding time point (T_n) will be noted on the eCRF. Each DOB will be plotted by the BreathID device using the following formula:

   $$DOB = {}^{13}CO_2/{}^{12}CO_2 @T_n - {}^{13}CO_2/{}^{12}CO_2 @T_0$$

   where T_0 is the baseline sample time (0) and T_n is the time point of the post-ingestion sample in minutes.
2. The DOBs will be transformed into percentage dose recovery rates (PDRs) at a specific time point (n) by using the following formula:

   $$PDR_n = 1.817853 * DOB_n \times w^{0.5378} \times h^{0.3963}$$

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

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

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

6.2.5 Child-Turcotte-Pugh Score

The Child-Turcotte-Pugh score provides an assessment of the prognosis of chronic liver disease. In this classification system, various laboratory and clinical parameters are scored as shown in Table 6-1.

Table 6-1 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 show in Table 6-2.

Table 6-2 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%

The subjects enrolled in this study will have Class A, well-compensated cirrhosis with a nearly 100% one-year survival. Additionally, a 2-point increase in the actual score will be used as an indication of progression of disease.

6.2.6 MELD 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 laboratory tests (serum bilirubin, serum creatinine, and prothrombin time 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)

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

6.2.7 EGD Evaluation

Subjects will undergo an EGD within 2 months prior to randomization and within 14 to 28 days after the final 26th dose of IMP or where feasible following study termination and the following information will be collected.

Esophageal varices, if present, will be classified as follows:

1. Large varices >50% impingement on the lumen;
2. Small varices <25% impingement on lumen;
3. Medium varices are intermediate between small and large varices.

Subjects with medium or large varices or varices with red signs, regardless of size, will be excluded from study participation. Red signs include red wale markings (dilated venules oriented longitudinally on the variceal surface), cherry red spots (small, red, spotty dilated venules usually about 2 mm in diameter on the variceal surface) or hematocystic spots (large, round, crimson red projection greater than 3 mm that looks like a blood blister on the variceal surface). Subjects without varices or with small varices will advance to HVPG measurement and liver biopsy. Consistent with the American Association for the Study of Liver Disease practice guidelines (Garcia-Tsao 2007), subjects with small varices will not receive treatment

with nonselective β-adrenergic inhibitors or variceal ligation therapy during the clinical study since long-term benefit has not been established for small varices. At the discretion of the principal investigator, subjects who have no varices or small varices and are currently on β-adrenergic inhibitors may be withdrawn from therapy at least 4 weeks prior to randomization.

6.3 Exploratory Assessments

6.3.1 Chronic Liver Disease Questionnaire

The CLDQ is a tool used to measure health-related quality of life in subjects with liver disease and has demonstrated good reliability and validity in subjects with chronic liver disease (Younossi 1999). The instrument includes 29 questions with 6 domains: abdominal symptoms, systemic symptoms, fatigue, activity, emotional function, and worry. The CLDQ will be given to the subject at the beginning of the visit (Table 12-2), and will be considered source documentation. The CLDQ is provided in Section 12.3.

6.3.2 Biomarkers

Blood will be collected for assessment of biomarkers (Table 12-2). Tests will include the ELF test, FibroTest (FibroSure), and galectin-3. At each of these times, a blood sample will be frozen (–20°C; –4°F) and held before treatment and at the end of treatment for other possible poststudy biomarker testing.

6.3.2.1 Enhanced Liver Fibrosis Test

The ELF is a method to predict the severity and clinical outcome in chronic liver diseases. The ELF test uses a routine blood sample to measure procollagen-III aminoterminal-propeptide, tissue inhibitor of matrix metalloproteinase-1, and hyaluronic acid.

6.3.2.2 FibroTest/FibroSure

The FibroTest score (FibroSure in the United States), is a composite score that has been correlated with the extent of liver fibrosis. This score is calculated from the subject's age,

sex, alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, γ-glutamyl transpeptidase, and total bilirubin.

6.3.2.3 Galectin-3

Blood will be collected for assessment of galectin-3 (Table 12-2).

6.3.3 Plasma and Serum Samples

Plasma and serum samples will be collected at Visits 1, 13, and 26 (Table 12-2). These samples will be stored at at –20°C.

6.4 Safety Assessments

All subjects receiving any part of at least 1 infusion of study treatment will be evaluated for safety. Safety assessments will include incidence of AEs during study treatment, emergent physical examination abnormalities, emergent vital sign and ECG abnormalities, and laboratory parameter abnormalities.

6.4.1 Vital Sign Measurements

Vital sign measurements (including heart and respiratory rate, blood pressure, and body temperature) will be collected before administration of IMP (Table 12-1 and Table 12-2).

Blood pressure will be obtained with the subject in the supine position and measured twice consecutively with a 1-minute interval between measurements. The average of the 2 measurements will be recorded.

6.4.2 Physical Examination

A complete physical examination, including height and weight, will be performed at screening, with particular attention to examination for stigmata of liver disease/cirrhosis (Table 12-1). A limited physical examination will only include weight and examination of the heart, lung, and abdomen during the treatment phase (Table 12-2).

6.4.3 Electrocardiogram

A standard 12-lead ECG will be performed during screening and the treatment phase (Table 12-1 and Table 12-2).

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

6.4.4 Chest Radiograph

Chest radiographs (posterior-anterior and lateral views) will be performed at screening (Table 12-1).

6.4.5 Adverse Events

6.4.5.1 Definitions of Adverse Events

The investigator is responsible for reporting all treatment-emergent AEs (TEAEs) that are observed or reported during the study, regardless of their relationship to IMP or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study, regardless of its causal relationship to IMP. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to IMP or any event already present that worsens in either intensity or frequency after exposure to IMP.

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring

intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.4.5.2 Eliciting and Documenting Adverse Events

All AEs (serious and nonserious) will be assessed beginning at screening and up to 42 days after the last dose of IMP.

Serious AEs that occur more than 42 days after the last dose of IMP need not be reported unless the investigator considers them related to IMP.

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs identified from any study data (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to subject safety will be documented on the AE page in the eCRF.

6.4.5.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to IMP, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA, Version 17.1) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the subject's condition deteriorates at any time during the study, it should be recorded as an AE.

Any AE that meets SAE criteria (Section 6.4.5.1) must be reported to the sponsor (designee) immediately (ie, within 24 hours) after the time study center personnel first learn about the event.

Study center personnel should complete the AE eCRF using electronic data capture, designating the event as serious. If electronic data capture is unavailable, complete an SAE form using the following contact information:

Pharmacovigilance
929 N Front St
Wilmington, NC 28401
SAE Hotline: 1-800-201-8725
SAE Fax line: 1-888-488-9697

6.4.5.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	These events require minimal or no treatment and do not interfere with the subject's daily activities.
Moderate:	These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.
Severe:	These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.5.5 Assessment of Causality

The investigator's assessment of an AE's relationship to IMP will be part of the documentation process, but it is not a factor in determining what is or is not reported in the

study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the IMP and the reported event.

Possible: This relationship suggests that treatment with the IMP caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of IMP administration or follows a known response pattern to the IMP, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with IMP administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the IMP seems likely. The event disappears or decreases on cessation or reduction of the dose of IMP.

Definite: This relationship suggests that a definite causal relationship exists between IMP administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the IMP is re-administered.

6.4.5.6 Exceptions

While the following events may fulfill the serious criteria, they do not need to be reported as SAEs: hospitalizations/emergency room stays lasting less than 24 hours not meeting other serious criteria, hospitalizations for baseline conditions that do not worsen after starting study participation, hospitalizations for elective procedures anticipated or scheduled prior to study participation, and events expected as part of progression of disease under study.

6.4.5.7 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable.

6.4.6 Pregnancy

Pregnancy is not regarded 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 using a clinical study pregnancy form. 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 subject 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 to PPD Pharmacovigilance by the study center within 24 hours of being informed of the event. If a pregnancy occurs during the study, study treatment must be discontinued immediately (or per sponsor directive), and the pregnancy report form submitted to PPD Pharmacovigilance via the SAE fax line. The study center should submit the pregnancy follow-up form to document the outcome of the pregnancy (health of the neonate). In the event of a miscarriage, therapeutic abortion, death in utero, or the pregnancy outcome leads to an SAE for the mother, follow the Procedure for Reporting an SAE (Section 6.4.5.3). In the event of a congenital anomaly, an SAE form for the baby must be completed.

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

6.4.7 Laboratory Analyses

Any abnormal laboratory test (hematology, clinical chemistry, or urinalysis) or other safety assessment results (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline, believed 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 subject's condition, are not to be reported as AEs or SAEs.

6.4.8 Hematology

Tests will include the following:

Hemoglobin
Hematocrit
Red blood cells
White blood cells
Red cell indices
Platelet count

Differential:
- Neutrophils
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils

Prothrombin time
Partial thromboplastin time
Haptoglobin

6.4.9 Blood Chemistry

Tests will include the following:

Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine
Fasting insulin level
γ-glutamyl transferase
Glucose
Lactate dehydrogenase
Magnesium
Phosphorus
Potassium
Sodium
Total and direct bilirubin
Total protein
Uric acid

6.4.10 Urinalysis

Refer to the Study Manual for collecting urinalysis samples. Tests will include the following:

Color
Clarity
pH
Specific gravity
Ketones
Protein
Glucose
Blood
Bilirubin
Leukocyte esterase
Nitrite
White blood cells
Red blood cells
Hyaline and other casts
Bacteria
Epithelial cells
Crystals
Yeast

6.4.11 Alcohol TLFB

Current alcohol consumption will be assessed during the treatment phase (Table 12-2) using the Alcohol TLFB. 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, subjects will provide retrospective estimates of their daily drinking over a specified time period. The Alcohol TLFB will be given to the subject at the beginning of the visit (Table 12-2), and will be considered source documentation.

Subjects should be instructed to refrain from regular alcohol use during the study. If subjects are found on the calendar to be drinking greater than or equal to 7 standard alcoholic drinks per week, they will be asked to stop drinking or reduce their intake. The Alcohol TLBF Calendars for the years 2015, 2016, and 2017 along with instructions are provided in Section 12.4.

6.5 Pharmacokinetic Assessments

Plasma levels of GR-MD-02 will be assessed in all subjects (Table 12-2). Plasma levels of GR-MD-02 will be assessed 2 hours following the infusion of IMP in all subjects after Infusion Visits 1, 2, 3, 4, 7 10, 13, and 26. At the first data safety monitoring board (DSMB) meeting, the panel will evaluate GR-MD-02 C_{max} plasma levels after Infusion Visits 1, 2, 3, and 4 for the first 30 subjects.

Blood samples for bioanalytical assay will be handled as described in the Study Manual. The date of PK blood collection must be recorded in the subject's eCRF. Each label will state the study number, subject number, matrix (plasma), and study day of the sample.

6.6 Sample Collections

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

7 Statistical and Analytical Plan

A summary of statistical methods is presented in the following sections and will be described in more detail in the statistical analysis plan (SAP).

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint analysis is the baseline-adjusted change in HVPG at 1 year (53-55 weeks) in subjects treated with placebo as compared to subjects treated with GR-MD-02 (2 mg/kg/week or 8 mg/kg/week).

7.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- The baseline-adjusted absolute change in the CPA at 1 year as determined by digital morphometric analysis of liver biopsies
- The baseline-adjusted change in liver stiffness as determined by FibroScan score prior to the first infusion, at Infusion Visit 13, and 14-28 days after final infusion
- The baseline-adjusted change in the metabolic capacity of the liver as determined by $cPDR_{30}$ of the MBT (if available) at screening, Infusion Visit 13, and 14-28 days after final infusion
- The difference between GR-MD-02-treated and placebo-treated subjects in the progression of cirrhosis at 1 year, defined as the development of any of the following:
  - esophageal variceal hemorrhage or portal hypertensive gastropathy hemorrhage (confirmed by endoscopy or interventional radiology)
  - clinically apparent ascites
  - spontaneous bacterial peritonitis
  - overt hepatic encephalopathy

- an increase in Child-Turcotte-Pugh score ≥2
- newly diagnosed varices in a subject without prior varices
- progression from small to medium or large varices
- qualification for liver transplant defined as a MELD score ≥15
- listing for a liver transplant or the performance of a liver transplant
- liver-related mortality

7.3 Exploratory Endpoints

Exploratory endpoints are to evaluate:

- Difference in health-related quality of life (using the subject-completed CLDQ) following administration of GR-MD-02 or placebo at 1 year
- Baseline-adjusted change in FibroTest (FibroSure) and ELF score at Infusion Visits 7, 13, 20, and 14-28 days after final infusion
- Changes in liver biopsy staining for alpha smooth muscle and galectin-3 in subjects treated with GR-MD-02 or placebo at 1 year
  - HVPG ≥10 and <15 mm Hg (elevated portal pressure, with potential development of varices, classified as clinically significant portal hypertension)
  - HVPG ≥15 (increased incidence of complications from varices)

7.4 Safety Endpoints

The safety endpoints include the incidence of AEs during study treatment, emergent physical examination abnormalities, emergent vital sign and ECG abnormalities, and laboratory parameter abnormalities.

7.5 Pharmacokinetic Endpoint

The PK endpoints include plasma concentrations and population PK parameters of GR-MD-02.

7.6 Sample Size Calculations

A total of approximately 156 subjects will be enrolled in the study. Sample size calculations are based on the comparison of the primary efficacy variable, change in HVPG from baseline, with the following assumptions (key assumptions discussed as follows):

1. True mean change in HVPG from baseline at 52 weeks in the placebo group, $\Delta p = 0$
2. True mean change in HVPG from baseline at 52 weeks in either GR-MD-02 dose group, $\Delta G = -2$ mm Hg
3. Common SD for difference in HVPG, $\sigma = 3$ mm Hg
4. Null hypothesis, H_0: $\theta = G - \Delta p = 0$
5. Type I error, $\alpha = 0.05$ (2-sided significance test)
6. Power = 80%
7. Statistical test = 2-sample *t* -test for mean difference
8. Randomization ratio = 1:1:1
9. Drop-out rate of 25%

For a mean difference of 2 mm Hg and accounting for a 25% dropout rate, the total sample size of 156 subjects (n = 52 subjects per group) will be required to achieve power of 80% with a 2-sided type I error rate of 0.05.

Discussion of assumptions:

1. True mean change in HVPG from baseline at 52 weeks in the placebo group was set at 0 mm Hg. While one might assume that the fibrosis would progress over a 1-year period and there might be a resultant increase in HVPG, the conservative assumption was made that there would be no change.

2. True mean change in HVPG from baseline at 52 weeks in either GR-MD-02 dose group was set at 2 mm Hg. A reduction of 2 mm Hg in HVPG was chosen because a change of this degree is likely to be of clinical significance. The results of pharmacological therapies, such as nonselective β-blockers have been remarkably consistent across therapeutic studies. If the HVPG is reduced by at least 20% from baseline, the risk of variceal bleeding, rebleeding, and other complications of portal hypertension such as ascites, spontaneous bacterial peritonitis and hepatorenal syndrome markedly decreases and survival improves (VillanuevaVillanueva 2009; Escorsell 2000; Abraldes 2003). In addition, a 10% reduction in HVPG has been shown to prevent the development of varices (Groszmann 2005). Therefore, it appears that a reduction in HVPG between 10% to 20% confers clinical benefit of reduced variceal bleeding. It is anticipated that the mean HVPG for the experimental groups will be between 10 mm Hg and 15 mm Hg, as in other similarly designed studies (Groszmann 2005). Therefore, a 2 mm Hg change in HVPG between placebo and treated groups would be between 15% and 20%, which is likely to be of clinical significance.

3. The common SD for difference in HVPG over 1 year for subjects in the placebo group was set at $\sigma = 3$ mm Hg. This assumption was determined from primary data, obtained from the investigator (Dr Guadalupe Garcia-Tsao), from a longitudinal clinical study (Groszmann 2005). Table 7-1 and Table 7-2 show data for subjects in the placebo group who had baseline and 12-month HVPG measurements (n = 82), of which 32 subjects had a baseline HVPG <10 mm Hg and 50 subjects had a baseline HVPG ≥10 mm Hg. From these data, the SD of the absolute change at 12 months in the placebo group was 2.85 mm Hg. Therefore, the assumption of 3 mm Hg for the sample size calculation appears valid.

Table 7-1 HVPG (mm Hg) at Baseline and 12 Months for Subjects in the Placebo Group in the Timolol Clinical Study

Treatment	Variable	N	Mean	SD	Median	Lower Quartile	Upper Quartile	Min	Max
Placebo	HVPG Baseline	82	11.29	3.97	10.75	8	14	6	23.5
Placebo	HVPG 12 mo	82	10.98	3.82	10.9	8	14	4	22.0

Abbreviations: Max, maximum; min, minimum; SD, standard deviation
Source: Groszmann 2005

Table 7-2 Absolute Change in HVPG (mm Hg) at 12 Months for Subjects in the Placebo Group in the Timolol Clinical Study

Treatment	N	Mean	SD	Median	Lower Quartile	Upper Quartile
Placebo	82	0.31	2.85	0.5	-1	2

Abbreviation: SD, standard deviation
Source: Groszmann 2005

7.7 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Full-Analysis set (FAS): The FAS, or intent-to-treat group, will consist of all subjects who were randomly assigned to IMP. All analyses using the FAS will group subjects according to randomized treatment. The FAS will be used as the primary efficacy analysis set.

Modified-Intent-to-Treat analysis set: The modified intent-to-treat set will consist of all subjects who were randomly assigned, received at least 1 infusion, and had at least 1 postbaseline efficacy assessment (from Section 6.2). All analyses using the modified intent-to-treat set will group subjects according to randomized treatment.

Per-protocol set: The per-protocol set will consist of all FAS subjects who have at least 80% compliance with study treatment, have not taken any prohibited medication, have no significant protocol deviations, and restricted to each subject's time on IMP plus 30 days thereafter for the analysis of progression of efficacy events. All analyses using the per-protocol set will group subjects according to treatment actually received.

Safety set: The safety set will consist of all subjects who received any IMP. All analyses using the safety set will group subjects according to treatment actually received.

Pharmacokinetic set: The PK analysis set will consist of subjects who provide at least 1 C_{max} PK sample.

7.8 Description of Subgroups to Be Analyzed

No subgroup analyses are planned.

7.9 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.1.3 or later. Continuous variables will be summarized by randomized treatment group using the mean, the SD, median, 25th and 75th percentiles, minimum value, and maximum value. Point estimates and the associated 95% confidence interval for the difference in baseline-adjusted efficacy parameters will be summarized in a similar manner. Categorical variables will be summarized by randomization treatment group using frequency counts and percentages. All baseline and postbaseline data used for safety and efficacy evaluations will be listed in data listings.

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

All statistical tests will be 2-sided and will be at the 5% level of significance. Due to the small number of subjects expected to be enrolled at each study center, all summaries and analyses will be performed using data pooled across study centers. Any imbalances in subject enrollment at study centers will be reviewed and methods for accommodating/eliminating the potential effect on efficacy analyses will be addressed in the SAP.

For analysis variables that are not normally distributed, alternative methods will be applied including the use of the Poisson-regression model (or the negative binomial) for counts data.

For others, a nonparametric method based on Hodge-Lehmann estimate (or similar) and associated 95% confidence interval on median difference will be applied (Hodges 1963).

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

Details of the statistical analyses, methods, adjustments for multiplicity, and data conventions will be described in the SAP.

7.9.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint analysis is the baseline-adjusted change in HVPG at 1 year (53 to 55 weeks) in subjects treated with placebo as compared to subjects treated with GR-MD-02 (2 mg/kg/week or 8 mg/kg/week). Change in HVPG from baseline will be compared between treatments groups using analysis of covariance adjusted for baseline HVPG. Treatment group will be included in the model as indicator variables where T1 = 1 if subject is randomly assigned to 2 mg/kg/week and 0 otherwise and T2 = 1 if subject is randomly assigned to 8 mg/kg/week and 0 otherwise. The following hypotheses will be tested based on the parameter estimates (and standard errors) from the fit of the analysis of covariance model:

H01: $\Delta T1 - \Delta p = 0$ vs HA1: $\Delta T1 - \Delta p \neq 0$

H02: $\Delta T2 - \Delta p = 0$ vs HA2: $\Delta T2 - \Delta p \neq 0$

The closed testing procedure of Bonferroni-Holm (1988) will be used to adjust for multiple comparisons of each GR-MD-02 dose (T1 and T2) with placebo so that overall type I error rate is preserved at 0.050 (2-sided). If at least 1 of 2 doses is found to be significantly better than placebo, the 2 doses will be compared with each other at the 0.05 level to address dose response.

7.9.2 Analysis of Key Secondary Efficacy Endpoints

Key secondary endpoints will be examined using a gatekeeper statistical approach. If the primary endpoint is significant ($\alpha < 0.05$), analysis will proceed to the secondary endpoints. Since the evaluation of secondary endpoints will proceed using a prespecified hierarchy without statistical correction for multiplicity, if a secondary endpoint does not meet statistical

significance, all subsequent analysis will be treated as exploratory only. The key secondary endpoints will be evaluated in the following sequence:

- Baseline-adjusted mean change in CPA will be compared between treatment groups using robust regression (M estimation method, Huber 1973) to account for skewedness of the data with adjustment for baseline CPA.
- The baseline-adjusted mean change in FibroScan at 1 year will be analyzed using similar methods previously defined for the primary efficacy endpoint
- The baseline-adjusted mean change in MBT (if available) at 1 year will be analyzed using similar methods previously defined for the primary efficacy endpoint
- The incidence of complications of cirrhosis with portal hypertension at 1 year will be compared between groups using chi-square analysis.

7.9.3 Analysis of the Exploratory Efficacy Endpoint

All exploratory endpoints will be analyzed in the same fashion as the primary endpoint.

7.9.4 Safety Analyses

All subjects receiving any part of at least 1 infusion of study treatment will be evaluated for safety. The safety analyses will include evaluation of the incidence of treatment-emergent adverse events (TEAEs), grade 3 or greater AEs, SAEs and AEs leading to discontinuation of study treatment using the Common Terminology Criteria for Adverse Events Version 4.0 or higher. Laboratory and vital sign measurement will be evaluated over time on study using descriptive statistics. Shift analyses of relevant clinical laboratory parameters will be produced showing shifts across low, normal, and high categories.

All heart rate (beats per minute), 12-lead ECG parameters, PR interval (milliseconds), QRS interval (milliseconds), QT interval (milliseconds), and QTc interval (milliseconds) will be measured, and overall interpretation will be summarized for all subjects by study visit including the last visit of the study.

Electrocardiogram parameters will be summarized using descriptive statistics. Mean and mean change from baseline values will be presented for every scheduled assessment. Change from baseline will be calculated as the postbaseline measurement minus the baseline measurement. If either the baseline or postbaseline value is missing, the observation will not be included in the change from baseline summary. In addition, counts and percentages for ECG overall interpretation (normal, abnormal, clinically significant, and not clinically significant) will be presented for each scheduled assessment.

For physical examinations, the results (normal, abnormal, or not done) by body system of the full physical examination at the randomization visit and follow-up visits will be summarized with descriptive statistics by treatment group and visit. For physical examinations performed at postrandomization time points, the number and percentage of subjects with no change or any significant changes since the previous examination will be presented by treatment received. In addition, a shift table will be included to summarize the number and percentage of subjects with changes from baseline to each postrandomization visit by body system for each treatment group. The number and percentage of subjects with normal and abnormal results (clinically significant versus not clinically significant) for each body system will be presented by treatment group.

Vital sign measurements (respiration, heart rate, temperature, systolic and diastolic blood pressure), height (at screening only), and BMI will be summarized descriptively at each scheduled visit. Mean and mean change from baseline values will be presented. Change from baseline will be calculated as postbaseline measurement minus baseline measurement. If either the baseline or postbaseline value is missing, the observation will not be included in the change from baseline summary.

All safety data will be listed by subject, parameter, and time point.

7.9.5 Pharmacokinetic Analyses

Pharmacokinetic data will be summarized descriptively. Descriptive statistics for GR-MD-02 concentrations by dose group and visit will include arithmetic mean, SD, coefficient of variation, minimum, median, maximum, geometric mean and coefficient of variation geometric mean as appropriate. If appropriate, data will be further stratified by age, gender, and/or other demographic variables. Standard graphics, including plots of arithmetic mean (+SD) concentration by dose group and visit (both linear and semi-logarithmic), overlay plots

of mean concentration and individual concentrations (both linear and semi-logarithmic) will be provided.

All concentrations below the limit of quantification or missing data will be labelled as such in concentration data listings. Concentrations below the lower limit of quantitation will be treated as zero in summary statistics of concentration data. All PK concentration data will be listed by subject and visit.

No statistical analyses of the pharmacokinetic data are planned. GR-MD-02 plasma levels will be used to evaluate systemic exposure following multiple dosing. Based on the high correlation between area under the concentration-time curve and C_{max} of GR-MD-02 in the Phase 1 clinical study (Galectin 2014), the plasma levels at 2 hours (approximate C_{max}) following the dose of GR-MD-02 will be used to estimate the systemic exposure and to assess the attainment of the steady state of GR-MD-02.

Exploratory population PK analysis will be performed. The nonlinear mixed-effect modeling approach will be used to evaluate the population pharmacokinetics of GR-MD-02. The population pharmacokinetic modeling will be performed using the NONMEM software (Icon Development Solutions, Hanover, MD).

The structural PK model will contain PK parameters such as clearance and volume of distribution as fixed-effect parameters. The intersubject variability in the parameter estimates and the random residual error in the data will be estimated with an appropriate error model. The best-fit model will be selected based on the standard criteria, such as objective function values and diagnostic plots. Covariates affecting the intersubject variability will be explored and, if possible, quantified. Pharmacokinetic data from the previous Phase 1 clinical study will be pooled with data from this study, if appropriate. The population pharmacokinetic analysis plan will be provided in an analysis plan.

7.9.6 Other Analyses

Summary statistical analyses will be provided for baseline assessments such as demographics and medical history.

The numbers and percentages of subjects in each treatment group taking concomitant medications, defined as nonstudy medications with a stop date on or after the date of the first

infusion of study treatment, will be summarized by dictionary coded terms (WHO Drug Dictionary (Version 1 Sep 2014). Medications that started prior to the first infusion of study treatment but continued during treatment will also be defined as concomitant. Ongoing medications without stop dates are considered concomitant. Prior medications, defined as nonstudy medications with a stop date before the first infusion of study treatment, will also be summarized by treatment group. Medications with partial onset/stop dates that indicate that the medication could be concomitant in relation to the start date of study treatment will be classified as concomitant. Otherwise, they will be classified as prior medications.

Investigational medicinal product exposure and overall percent compliance will be calculated per subject in the FAS population and summarized by treatment group using descriptive statistics.

Additional exploratory analyses for the MBT (if available): A model/algorithm will be developed to increase correlation with HVPG measurements and biopsy results.

All available breath test parameters (DOB at the respective times) will be collected from the completed eCRFs. The DOBs will be transformed to PDR by normalizing the DOB using subject weight and height (see Section 6.2.4). The area under the DOB and under the PDR curve will be calculated for a 5-minute time interval resulting in cDOB and cPDR at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 minutes, respectively. The algorithm will be developed using either logistic regression or neural network or any other known methodology including all available breath test parameters, as well as subject demographic and laboratory data. Using a cut-point on the score, a binary diagnosis of (yes/no) will be obtained for several HVPG cut-offs, as well as histological scores. Cross-validation methods will be used to test algorithm stability.

7.9.7 Interim Analyses

An interim analysis of PK data will be conducted for the DSMB meeting as outlined in Section 10.1.1: Independent Data Safety Monitoring Board.

7.10 Data Quality Assurance

The sponsor's (or an authorized representative's) Quality Assurance Department may conduct on-site audits of all aspects of the clinical study either during the study or after the study has been completed.

The clinical study may also be subject to inspection by regulatory authorities (national or foreign), as well as the institutional review board/independent ethics committee (IRB/IEC) to ascertain that the study is being or has been conducted in accordance with protocol requirements, Good Clinical Practice (GCP), as well as the applicable regulatory requirements.

7.10.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include hospital records, clinical and office charts, chest x-ray and interpretation, questionnaires, pharmacy dispensing, and other records.

The eCRF will be supplied by PPD. All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed. Corrections to the eCRF will be entered in the eCRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the electronic system. For corrections made via data queries, a reason for any alteration must be provided.

The CRF data for this study will be collected with an electronic data capture tool, Medidata RAVE. Each completed eCRF must be reviewed, signed, and dated by the investigator in a timely manner. The completed eCRF will be collected by clinical monitors as soon as practical after completion.

Clinical data management will be performed in accordance with applicable Galectin Therapeutics Inc standards and data cleaning procedures to ensure the integrity of the data,

eg, removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using MedDRA, an internal validated medication dictionary.

After database lock, each study center will receive a CDROM containing all of their study center-specific eCRF data as entered into Medidata RAVE for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all of the study center's data will be created and sent to the sponsor for storage. A duplicate CDROM copy will be maintained by PPD for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1): Good Clinical Practice require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH E6(R1): GCP will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R1) GCP, and all applicable regulations.

8.3 Subject Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to investigative study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the sponsor or its designee or both before

IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed and dated ICF to the subject or legal guardian.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and governmental standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the US FDA, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the subject's disease.

9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and 21 CFR 50 by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinicaltrials.gov before enrollment of subjects begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol and in accordance with ICH E6(R1) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to the study center IRB/IEC, as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH E6(R1) region and until there are no pending or contemplated marketing applications in an ICH E6(R1) region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

10 Study Management

10.1 Monitoring

10.1.1 Independent Data Safety Monitoring Board

A DSMB will be established that includes a panel of at least 3 independent members to include medical experts and an unblinded biostatistician. An official 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 DSMB or Galectin Therapeutics Inc that such a review is warranted. An organizational meeting will be held prior to the first subject randomly assigned to IMP to review and approve the DSMB Charter and to review the output to be provided to the DSMB for scheduled reviews. In addition, an unblinded monitoring team will be established.

The first scheduled DSMB review meeting will be after the first 30 subjects in the study have received 7 doses of IMP. The purpose of this early look at safety is to ensure that there are no unexpected AEs in the population being evaluated in this study. The second scheduled DSMB review meeting will occur after approximately 50% of the total number of subjects to be enrolled has received 13 doses of IMP. The DSMB will then meet again after 50% of subjects have received 26 doses of IMP.

At the first DSMB meeting, the panel will also evaluate GR-MD-02 C_{max} plasma levels after Infusion Visits 1, 2, 3, and 4 for the first 30 subjects. There should be approximately 10 subjects who received 2 mg/kg and 10 subjects who received 8 mg/kg in this group of subjects. With the aid of a clinical pharmacologist on the panel, the DSMB will assess C_{max} levels as a surrogate for systemic exposure, with increasing number of doses in the groups receiving IMP and compare the levels to the safety margins indicated by long-term animal toxicology studies.

The investigative study center staff, subjects, 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.

10.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to closely follow the study. In doing so, the monitor will visit the investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable governmental regulation with respect to current GCP and current standard operating procedures.

For the purposes of this study, a blinded and unblinded monitoring team will be used.

10.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator’s IRB/IEC for approval before subjects can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without prior sponsor approval, or nonadherence to FDA regulations or ICH E6(R1) GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

Although Galectin Therapeutics Inc has every intention of completing the study, Galectin Therapeutics Inc reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies), as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study

reports in marketing applications meet the standards of the ICH E6(R1): Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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12 Appendices

12.1 Appendix: Schedule of Events

Table 12-1 Schedule of Events - Prescreening and Screening

Procedure	**Prescreening**	**Screening**
Week	**Week –9**	**Week -8 to Day 0[a]**
IWRS	X	X
Informed consent	X	
NASH Diagnosis	X[b]	
FibroScan	X[b]	
Inclusion/exclusion criteria		X
AUDIT		X
Demographic information		X
Medical, surgical, medication history		X
12-lead ECG		X
Hematology		X[c]
Blood chemistry		X[d]
Coagulation profile		X
MELD score		X
Viral hepatitis B and C serology		X
HIV serology		X
Urine drug screen (amphetamines, cocaine, and nonprescription opiates)		X
Urinalysis		X[e]
Serum pregnancy test (females of childbearing potential only)		X[f]
Chest radiographs (posterior-anterior and lateral views)		X
Child-Turcotte-Pugh score		X
Complete physical examination		X[g]

Table 12-1 Schedule of Events - Prescreening and Screening, Continued

Procedure	Prescreening	Screening
Week	**Week –9**	**Week -8 to Day 0[a]**
Vital sign measurements		X[h]
MBT (if available)		X[i]
EGD		X[j]
HVPG		X[k]
Liver biopsy		X
AE monitoring		X

Abbreviations: AE, adverse event; AUDIT, Alcohol Use Disorders Identification Test; ECG, electrocardiogram; EGD, esophagogastroduodenoscopy; HIV, human immunodeficiency virus; HVPG, hepatic venous pressure gradient; IWRS, interactive web response system; MBT, ^{13}C-methacetin breath test; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis.

[a] The screening visit window is up to 8 weeks. Subjects who fail to meet eligibility criteria during the screening period due to an abnormal laboratory result may undergo retesting of the abnormal laboratory parameter during the screening window and at the discretion of the investigator and with prior approval of the medical monitor.

[b] Subjects who have had a previous liver biopsy with either advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6) are eligible to move forward to screening. Subjects with a presumptive clinical diagnosis of NASH (based on the assessment of the principal investigator) will have a FibroScan to assess the potential for fibrosis. Subjects who have a FibroScan score of ≥12.0 kPa will be considered to have advanced fibrosis and will proceed to screening. Likewise, subjects with a documented qualifying FibroScan score within the previous 12 months of screening may proceed to screening.

[c] Hematology will include complete blood cell count with differential (red blood cells, white blood cells, red cell indices, platelets, hemoglobin, and hematocrit).

[d] 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, γ-glutamyl transferase, and fasting insulin level. Subjects must be in a fasted state prior to blood collection.

[e] 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.

[f] Serum pregnancy test for females of childbearing potential only. (A urine pregnancy test will be given every 4 weeks during the treatment phase.)

[g] Including height (in cm) and weight (in kg) with particular attention to examination for stigmata of liver disease/cirrhosis).

[h] Vital sign measurements include heart and respiratory rate, blood pressure, and body temperature. Blood pressure will be obtained with the subject in the supine position and measured twice consecutively with a 1-minute interval between measurements. The average of the 2 measurements will be recorded.

[i] The MBT (if available) will be performed prior to EGD, HVPG, or liver biopsy (at the discretion of the investigator). The study center will make a follow-up telephone call to the subject to capture any AEs that may have occurred within 48 hours after the breath test.

j Subjects will have had an EGD within 2 months prior to randomization. Subjects with medium or large varices or varices with red signs (red wale marks or red spots), regardless of size, will be excluded from study participation. Subjects without varices or with small varices will continue to HVPG measurement and liver biopsy.

[k] Subjects must have both an HVPG measurement ≥6 mm Hg and a liver biopsy with advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6), presumably due to NASH. Subjects without varices or with small varices will have hepatic venous catheterization with measurement of both wedged and free hepatic venous pressures and standardized calculation of the HVPG prior to randomization and first IMP infusion.

Table 12-2 Schedule of Events - Randomization, Treatment Phase, and Follow-up/Early Termination

Infusion Visit	**0**	**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**	**14-28 Days After Final Dose**	**14 Days After Previous Visit/ET**
Week ± 3 days		**1**	**3, 5, 7, 9, 11**	**13**	**15, 17, 19, 21, 23**	**25**	**27, 29, 31, 33, 35, 37**	**39**	**41**	**43, 45, 47, 49**	**51**	**53-55**	**57**
IWRS	R A N D O M I Z A T I O N	X	X	X	X	X	X	X	X	X	X	X	X
FibroScan		X[a]				X						X	
MBT (if available)						X						X	
CLDQ[b]		X									X		
Alcohol TLFB [b]		X	X - Inf Visit 5		X - Inf Visit 9	X	X - Inf Visit 17		X	X - Inf Visit 25			
Limited physical examination[c]		X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[d]			X - Inf Visits 3, 5	X	X - Inf Visits 9, 11	X	X - Inf Visits 15, 17, 19		X	X - Inf Visits 23, 25			
Vital sign measurements[e]		X	X	X	X	X	X	X	X	X	X	X	X
Hematology[f]		X		X		X		X			X	X	
Blood chemistry[g]		X		X		X		X			X	X	
MELD score						X					X		
Biomarkers blood sample[h]		X				X						X	
Plasma and serum sample for storage		X				X					X		
IMP administration[i]		X	X	X	X	X	X	X	X	X	X		
12-lead ECG						X							X
Child-Turcotte-Pugh score						X					X		
EGD[j]												X	
HVPG[j]												X	

Table 12-2 Schedule of Events - Randomization, Treatment Phase, and Follow-up/Early Termination, Continued

Infusion Visit	**0**	**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**	**14-28 Days After Final Dose**	**14 Days After Previous Visit/ET**
Week ± 3 days		**1**	**3, 5, 7, 9, 11**	**13**	**15, 17, 19, 21, 23**	**25**	**27, 29, 31, 33, 35, 37**	**39**	**41**	**43, 45, 47, 49**	**51**	**53-55**	**57**
Liver biopsy[j]												X	
Assessment of cirrhosis complications			X - Inf Visits 3, 5	X	X - Inf Visits 9, 11	X	X - Inf Visits 15, 17, 19		X	X - Inf Visits 23, 25	X		
AE monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
PK sample[k]		X	X - Inf Visits 2, 3, 4	X	X - Inf Visit 10	X					X		

Abbreviations: AE, adverse event; TLFB, Timeline Followback; EGD, esophagogastroduodenoscopy; CLDQ, chronic liver disease questionnaire; ECG, electrocardiogram; ET, early termination; HVPG, hepatic venous pressure gradient; IMP, investigational medicinal product; Inf, infusion; IWRS, interactive web response system; MBT, ^{13}C-methacetin breath test; MELD, model for end-stage liver disease; PK, pharmacokinetic.

Note: Subjects will be entered into the study and randomly assigned to IMP if they have both an HVPG screening measurement ≥6 mm Hg and a liver biopsy with advanced bridging fibrosis (Ishak stage 4) or cirrhosis (Ishak stage 5 or 6) presumably due to NASH.

Note: Acceptable treatment windows for infusions will be ± 3 days. Infusions given outside of accepted windows will be considered "out-of-window" doses. If a dose is out of window, the subject should be brought back into compliance with their visit dosing schedule. The subject should not dose within 7 days of the previous or next dose unless the medical monitor is consulted.

Note: Randomization must occur prior to Infusion Visit 1.

[a] Within 2 weeks prior to the first infusion.

[b] To be administered at the beginning of the visit.

[c] Limited physical examination includes weight and examination of the heart, lung, and abdomen.

[d] Urine pregnancy test will be given to females of childbearing potential every 4 weeks during the treatment phase

[e] Vital sign measurements include heart and respiratory rate, blood pressure and body temperature prior to IMP administration. Blood pressure will be obtained with the subject in the supine position and measured twice consecutively with a 1-minute interval between measurements. The average of the 2 measurements will be recorded.

[f] Hematology will include complete blood cell count with differential (red blood cells, white blood cells, , red cell indices, platelets, hemoglobin, and hematocrit).

[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, γ-glutamyl transferase, and fasting insulin level. Subjects must be in a fasted state prior to blood collection.

[h] Biomarker blood tests will include the enhanced liver fibrosis test, FibroTest (FibroSure), and galectin-3 and will occur prior to first infusion and at Infusion Visits 13 and 14 to 28 days following final 26th infusion.

[i] IMP administration will occur after the following procedures: limited physical examination, vital sign measurements, hematology, blood chemistry, and biomarker blood samples.

[j] Within 14 to 28 days after the final 26th dose of IMP or where feasible following study termination due to the occurrence of a clinical event or withdrawal of consent. EGD must be performed on a different day within the 14- to 28-day follow-up period than when the HVPG assessment is performed.

[k] The PK sample will be collected 2 hours after the end of the IMP infusion.

Table 12-3 Schedule of Events - End-of-Study Telephone Contact[a]

Assessment	Year 1 Months 6, 12	Year 2 Months 18, 24	Year 3 Month 36	Year 4 Month 48
Survival	X	X X X		
Listing for a liver transplant	X	X	X	X
Performance of a liver transplant[a]	X	X X X		
Complications of chronic liver disease[b]	X	X X X		

[a] For those subjects who do not enroll in the open-label extension study.

[b] Telephone contact will discontinue if a subject undergoes a liver transplant.

[c] Complications of chronic liver disease include ascites, spontaneous bacterial peritonitis, variceal bleeding, and encephalopathy.

12.2 Appendix: The AUDIT Questionnaire

The full AUDIT manual will be provided in the Study Manual.

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/.

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	

12.3 Appendix: The Chronic Liver Disease Questionnaire

The Chronic Liver Disease Questionnaire (CLDQ)

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 two 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 two 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 two 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

Revised December 28, 1998

5. How much of the time during the last two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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

Revised December 28, 1998

20. How much of the time during the last two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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 two 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

Questionnaire sur la maladie chronique du foie

(Chronic Liver Disease Questionnaire, CLDQ)

Ce questionnaire est conçu pour comprendre comment vous vous êtes senti au cours des deux dernières semaines. On vous posera des questions concernant des symptômes associés à votre maladie du foie, concernant comment vous avez été affecté dans vos activités, et comment votre humeur s'en est vue changer. Veuillez compléter toutes les questions et ne sélectionner **qu'une seule** réponse pour chaque question.

1. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous senti affecté par un ventre gonflé?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

2. Pendant combien de temps vous êtes-vous senti fatigué au cours des deux dernières semaines?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

3. Au cours des 2 dernières semaines, pendant combien de temps avez-vous ressenti une douleur physique?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

4. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous senti fatigué pendant la journée?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

Révisée 28 décembre 1998

5. Au cours des deux dernières semaines, pendant combien de temps avez-vous ressenti une douleur abdominale?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

6. Au cours des deux dernières semaines, avez-vous eu le souffle court pendant vos activités quotidiennes?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

7. Au cours des deux dernières semaines, n'avez-vous pas été en mesure de manger autant que vous l'auriez souhaité?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

8. Au cours des deux premières semaines, pendant combien de temps avez-vous été affecté par un manque de puissance physique?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

9. Au cours des 2 dernières semaines, à quelle fréquence avez-vous rencontré des difficultés pour transporter des objets lourds?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

10. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous senti anxieux pendant la journée?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

11. Au cours des 2 dernières semaines, à quelle fréquence vous êtes-vous senti comme étant affecté par une diminution du niveau d'énergie?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

12. Pendant combien de temps vous êtes-vous senti malheureux au cours des deux dernières semaines?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

13. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous senti somnolent au cours de la journée?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

14. Au cours des deux dernières semaines, à quelle fréquence avez-vous été empêché par une limite de votre diète?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

15. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous senti irritable au cours de la journée?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

16. Au cours des deux dernières semaines, pendant combien de temps avez-vous eu de la difficulté à dormir pendant la nuit?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

17. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous senti affligé d'un inconfort abdominal?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

18. Au cours des deux dernières semaines, à quel point avez-vous été inquiet de l'impact de la maladie sur votre famille?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

19. Pendant combien de temps vous êtes-vous senti malheureux au cours des deux dernières semaines? Avez-vous réussi à amener un marbre qui donne du charme à cet endroit vide de la maison.

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

20. Au cours des deux dernières semaines, pendant combien de temps avez-vous été incapable de dormir pendant la nuit?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

21. Au cours des deux dernières semaines, à quelle fréquence avez-vous eu des crampes musculaires?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

22. Au cours des deux dernières semaines, combien de temps avez-vous été inquiété de voir vos symptômes se développer en problèmes majeurs?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

23. Pendant combien de temps avez-vous senti que votre gorge était sèche?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

24. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous senti déprimé?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

25. Au cours des deux dernières semaines, à quel intervalle vous êtes-vous inquiété de voir votre situation empirer?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

26. Pendant combien de temps avez-vous senti que vous aviez des problèmes de concentration?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

27. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous senti importuné par des démangeaisons?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

28. Au cours des deux dernières semaines, vous êtes-vous inquiété de ne jamais vous sentir mieux qu'à ce moment?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

29. Au cours des deux dernières semaines, pendant combien de temps vous êtes-vous inquiété de recevoir une transplantation dont vous aviez besoin?

1 Tout le temps
2 La plupart du temps
3 Une bonne partie du temps
4 Une partie du temps
5 Quelque peu pendant cette période
6 À peine
7 En aucun temps

Cuestionario sobre la enfermedad hepática crónica (CLDQ, por su sigla en inglés)

Este cuestionario está diseñado para averiguar cómo se ha sentido durante las últimas dos semanas. Se le harán preguntas sobre los síntomas que ha sufrido a causa de su enfermedad hepática, sobre cómo se han visto afectadas sus actividades cotidianas y sobre su estado de ánimo. Complete todas las preguntas y seleccione sólo **una** respuesta para cada pregunta.

1. Durante las últimas dos semanas ¿con qué frecuencia ha sufrido molestias a causa de una sensación de distensión abdominal?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

2. Durante las últimas dos semanas ¿con qué frecuencia se ha sentido cansado o fatigado?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

3. **Durante las últimas dos semanas ¿con qué frecuencia ha sentido dolor corporal?**

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

4. Durante las últimas dos semanas ¿con qué frecuencia se ha sentido somnoliento durante el día?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

Revisado el 28 de diciembre de 1998

5. Durante las últimas dos semanas ¿con qué frecuencia ha sentido dolor abdominal?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

6. Durante las últimas dos semanas ¿con qué frecuencia la falta de aliento le ha dificultado la realización de sus actividades cotidianas?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

7. Durante las últimas dos semanas ¿con qué frecuencia no ha podido comer todo lo que hubiera querido?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

8. Durante las últimas dos semanas ¿con qué frecuencia ha sufrido molestias a causa de una sensación de debilidad?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

9. Durante las últimas dos semanas ¿con qué frecuencia ha tenido inconvenientes al levantar o transportar objetos pesados?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces

6 Casi nunca
7 Nunca

10. Durante las últimas dos semanas ¿con qué frecuencia se ha sentido ansioso?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

11. Durante las últimas dos semanas ¿con qué frecuencia se ha sentido débil?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

12. Durante las últimas dos semanas ¿con qué frecuencia se ha sentido triste?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

13. Durante las últimas dos semanas ¿con qué frecuencia se ha sentido somnoliento?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

14. Durante las últimas dos semanas ¿con qué frecuencia se ha sentido molesto **a causa de una limitación en su dieta?**

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca

7 Nunca

15. Durante las últimas dos semanas ¿con qué frecuencia ha estado irritable?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

16. Durante las últimas dos semanas ¿con qué frecuencia ha tenido dificultad para dormir por la noche?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

17. Durante las últimas dos semanas ¿con qué frecuencia ha sufrido molestias a causa de una sensación de malestar abdominal?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

18. Durante las últimas dos semanas ¿con qué frecuencia ha estado preocupado por la repercusión que tiene su enfermedad hepática en su familia?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

19. Durante las últimas dos semanas ¿con qué frecuencia ha sufrido cambios bruscos de ánimo?

1 Siempre
2 La mayor parte del tiempo

3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

20. Durante las últimas dos semanas ¿con qué frecuencia no ha podido quedarse dormido por la noche?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

21. Durante las últimas dos semanas ¿con qué frecuencia ha sufrido calambres musculares?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

22. Durante las últimas dos semanas ¿con qué frecuencia ha estado preocupado por la posibilidad de que sus síntomas se conviertan en problemas más graves?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

23. Durante las últimas dos semanas ¿con qué frecuencia ha tenido la boca reseca?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

24. Durante las últimas dos semanas ¿con qué frecuencia se ha sentido deprimido?

1 Siempre
2 La mayor parte del tiempo

3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

25. Durante las últimas dos semanas ¿con qué frecuencia ha estado preocupado por la posibilidad de que su enfermedad empeore?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

26. Durante las últimas dos semanas ¿con qué frecuencia ha tenido dificultad para concentrarse?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

27. Durante las últimas dos semanas ¿con qué frecuencia ha sufrido molestias a causa de picazón?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

28. Durante las últimas dos semanas ¿con qué frecuencia ha estado preocupado por la posibilidad de que usted nunca se sienta mejor?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

29. Durante las últimas dos semanas ¿con qué frecuencia ha estado preocupado por la disponibilidad de un hígado si usted llegara a necesitar un trasplante?

1 Siempre
2 La mayor parte del tiempo
3 Una buena parte del tiempo
4 Algunas veces
5 Muy pocas veces
6 Casi nunca
7 Nunca

12.4 Alcohol TLFB

Sobell LC, Maisto SA, Sobell MB, et al. Reliability of alcohol abusers' self-reports of drinking behavior. Behav Res Ther. 1979;17(2):157-60.

Sobell LC, Sobell MB. Timeline Follow-back: A technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP (editors). Measuring alcohol consumption: Psychosocial and biochemical methods. Humana; -Totowa, NJ: 1992. P. 41-72.

Sobell LC and Sobell MB. Alcohol Timeline Followback (TLFB) Users' Manual. Toronto: Addiction Research Foundation, 1995.

12.4.1 Alcohol TLFB Calendar 2015

Name/ID#: _____ Date: _____

TIMELINE FOLLOWBACK CALENDAR: 2015

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

2015	SUN	MON	TUES	WED	THURS	FRI	SAT
					1 New Year's Day	2	3
J	4	5	6	7	8	9	10
A	11	12	13	14	15	16	17
N	18	19 M. Luther King	20	21	22	23	24
	25	26	27	28	29	30	31
F	1	2	3	4	5	6	7
E	8	9	10	11	12	13	14 Valentine's Day
B	15	16 Pres. Day	17	18	19 Chinese New Yr	20	21
	22	23	24	25	26	27	28
M	1	2	3	4	5	6	7
A	8	9	10	11	12	13	14
R	15	16	17 St. Patrick's Day	18	19	20	21
	22	23	24	25	26	27	28
	29	30	31	1	2	3 Passover	4 Good Friday
A	5 Easter	6	7	8	9	10	11
P	12	13	14	15	16	17	18
R	19	20	21	22	23	24	25
	26	27	28	29	30	1	2
M	3	4	5	6	7	8	9
A	10 Mother's Day	11	12	13	14	15	16
Y	17	18	19	20	21	22	23
	24	25 Memorial Day	26	27	28	29	30
	31						

2015	SUN	MON	TUES	WED	THURS	FRI	SAT
		1	2	3	4	5	6
J	7	8	9	10	11	12	13
U	14	15	16	17	18	19	20
N	21 Father's Day	22	23	24	25	26	27
	28	29	30	1	2	3	4 Independence Day
J	5	6	7	8	9	10	11
U	12	13	14	15	16	17	18
L	19	20	21	22	23	24	25
	26	27	28	29	30	31	1
A	2	3	4	5	6	7	8
U	9	10	11	12	13	14	15
G	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30	31	1	2	3	4	5
S	6	7 Labor Day	8	9	10	11	12
E	13 Rosh Hashanah	14	15	16	17	18	19 Rosh Hashanah
P	20	21	22 Yom Kippur	23	24	25	26
	27	28	29	30	1	2	3
O	4	5	6	7	8	9	10
C	11	12 Columbus Day	13	14	15	16	17
T	18	19	20	21	22	23	24
	25	26	27	28	29	30	31 Halloween
N	1	2	3 Election Day	4	5	6	7
O	8	9	10	11 Veterans Day	12	13	14
V	15	16	17	18	19	20	21
	22	23	24	25	26 Thanksgiving	27	28
	29	30	1	2	3	4	5
D	6 Hanukkah	7	8	9	10	11	12
E	13	14	15	16	17	18	19
C	20	21	22	23	24	25 Christmas	26
	27	28	29	30	31 New Year's Eve		

12.4.2 Alcohol TLFB Calendar 2016

Name/ID#: _____ Date: _____

TIMELINE FOLLOWBACK CALENDAR: 2016

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

2016	SUN	MON	TUES	WED	THURS	FRI	SAT
						1 New Year's	2
J	3	4	5	6	7	8 Chinese New Yr	9
A	10	11	12	13	14	15	16
N	17	18 M. Luther King	19	20	21	22	23
	24	25	26	27	28	29	30
	31	1	2	3	4	5	6
F	7	8	9	10	11	12	13
E	14 Valentine's Day	15 President's Day	16	17	18	19	20
B	21	22	23	24	25	26	27
	28	29 Leap Year	1	2	3	4	5
M	6	7	8	9	10	11	12
A	13	14	15	16	17 St.Patrick's Day	18	19
R	20	21	22	23	24	25 Good Friday	26
	27 Easter Sunday	28	29	39	31	1	2
A	3	4	5	6	7	8	9
P	10	11	12	13	14	15	15
R	17	18	19	20	21	22 Passover	23
	24	25	26	27	28	29	30
M	1	2	3	4	5	6	7
A	8 Mother's Day	9	10	11	12	13	14
Y	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30 Memorial Day	31				

2016	SUN	MON	TUES	WED	THURS	FRI	SAT
				1	2	3	4
J	5	6	7	8	9	10	11
U	12	13	14	15	16	17	18
N	19 Father's Day	20	21	22	23	24	25
26	26	27	28	29	30	1	2
J	3	4 Independence Day	5	6	7	8	19
U	10	11	12	13	14	15	16
L	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
A	31	1	2	3	4	5	6
U	7	8	9	10	11	12	13
G	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
	28	29	30	31	1	2	3
S	4	5	6	7	8	9	10
E	11	12	13	14	15	16	17
P	18	19	20	21	22	23	24
	25	26	27	28	29	30	1
O	2 Rosh Hashanah	3	4	5	6	7	8
C	9	10	11	12 Yom Kippur	13	14	15
T	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30	31 Halloween	1	2	3	4	5
N	6	7	8 Election Day	9	10	11 Veterans' Day	12
O	13	14 Columbus Day	15	16	17	18	19
V	20	21	22	23	24 Thanksgiving	25	26
	27	28	29	30	1	2	3
D	4	5	6	7	8	9	10
E	11	12	13	14	15	16	17
C	18	19	20	21	22	23	24 Hanukkah
	25 Christmas	26	27	28	29	30	31 New Year's Eve

12.4.3 Alcohol TLFB Calendar 2017

Name/ID#: _____ Date: _____

TIMELINE FOLLOWBACK CALENDAR: 2017

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

2017	SUN	MON	TUES	WED	THURS	FRI	SAT
	1 New Year's	2	3 4 5 6 7				
J	8	9	10	11	12	13	14
A	15	16 M. L. King	17	18	19	20	21
N	22	23	24	25	26	27	28 Chinese New Yr
	29	30	31	1	2	3	4
F	5	6 7 8 9 1				0	11
E	12	13	14 Valentine's Day	15	16	17	18
B	19	20 Presidents' Day	21	22	23	24	25
	26	27	28	1	2	3 4	
M	5	6 7 8 9 1				0	11
A	12	13	14	15	16	17 St. Patrick's Day	18
R	19	20	21	22	23	24	25
	26	27	28	29	30	31	1
A	2	3 4		5	6 7		8
P	9	10	11 Passover	12	13	14 Good Friday	15
R	16 Easter	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30	1	2 3 4 5 6				
M	7	8	9	10	11	12	13
A	14 Mother's Day	15	16	17	18	19	20
Y	21	22	23	24	25	26	27
	28	29 Memorial Day	30	31			

2017	SUN	MON	TUES	WED	THURS	FRI	SAT
					1	2 3	
J	4	5 6 7 8 9 1					0
U	11	12	13	14	15	16	17
N	18 Father's Day	19	20	21	22	23	24
	25	26	27	28	29	30	1
J	2	3 4	July 4th	5	6 7 8		
U	9	10	11	12	13	14	15
L	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30	31	1	2 3 4 5			
A	6	7 8 9 1			0	11	12
U	13	14	15	16	17	18	19
G	20	21	22	23	24	25	26
	27	28	29	30	31	1	2
S	3	4 Labor Day	5	6 7 8 9			
E	10	11	12	13	14	15	16
P	17	18	19	20	21	22	23
	24	25	26	27	28	29	30 Rosh Hashanah
O	1	2	3	4 5 6 7			
C	8	9 Columbus Day	10	11	12	13	14
T	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30 Yom Kippur	31 Halloween	1	2	3 4	
N	5	6 7 8 9 1				0	11 Veterans Day
O	12	13	14	15	16	17	18
V	19	20	21	22	23 Thanksgiving	24	25
	26	27	28	29	30	1	2
D	3	4 5 6			7	8 9	
E	10	11	12 Hanukkah	13	14	15	16
C	17	18	19	20	21	22	23
	24	25 Christmas	26	27	28	29	30
	31 New Years Eve						

12.4.4 Instructions for Completing the Alcohol TLFB

Instructions for Filling Out the Timeline Alcohol Use Calendar

To help us evaluate your drinking, we need to get an idea of what your alcohol use was like in the past ____ days. To do this, we would like you to fill out the attached calendar.

- ✓ Filling out the calendar is not hard!
- ✓ Try to be as accurate as possible.
- ✓ We recognize you won't have perfect recall. That's OKAY.

✓ WHAT TO FILL IN

- The idea is to put a number in for **each day** on the calendar.
- On days when you did not drink, you should write a "0".
- On days when you did drink, you should write in the total number of drinks you had.
- We want you to record your drinking on the calendar using Standard Drinks. *For example,* if you had 6 beers, write the number 6 for that day. If you drank two or more different kinds of alcoholic beverages in a day such as 2 beers and 3 glasses of wine, you would write the number 5 for that day.

It's important that something is written for <u>every</u> day, even if it is a "0".

✓ YOUR BEST ESTIMATE

- We realize it isn't easy to recall things with 100% accuracy.
- If you are not sure whether you drank 7 or 11 drinks or whether you drank on a Thursday or a Friday, **give it your best guess!** What is important is that 7 or 11 drinks is very different from 1 or 2 drinks or 25 drinks. The goal is to get a sense of how frequently you drank, how much you drank, and your patterns of drinking.

✓ HELPFUL HINTS

- If you have an appointment book you can use it to help you recall your drinking.
- Holidays such as Thanksgiving and Christmas are marked on the calendar to help you better recall your drinking. Also, think about how much you drank on personal holidays & events such as birthdays, vacations, or parties.
- If you have regular drinking patterns you can use these to help you recall your drinking. For example, you may have a daily or weekend/weekday pattern, or drink more in the summer or on trips, or you may drink on Wednesdays after playing sports.

✓ COMPLETING THE CALENDAR

- A blank calendar is attached. Write in the number of Standard Drinks that you had each day.
- The time period we are talking about on the calendar is **from _____ to _____.**
- In estimating your drinking, be as accurate as possible.
- **DOUBLE CHECK THAT <u>ALL</u> DAYS ARE FILLED IN BEFORE RETURNING THE CALENDAR.**
- Before you start look at the **SAMPLE CALENDAR AND STANDARD DRINK CHART** on the next page.

Instructions for Filling Out the Timeline Alcohol Use Calendar

✓ SAMPLE CALENDAR

2000	SUN	MON	TUES	WED	THURS	FRI	SAT
						1 8	2 0
S	3 7	4 Labor Day 0	5 3	6 8	7 1	8 0	9 11
E	10 2	11 2	12 0	13 3	14 5	15 14	16 4
P	17 2	18 0	19 0	20 0	21 0	22 2	23 13
T	24 0	25 0	26 6	27 0	28 0	29 0	30 2

U. S. STANDARD DRINK CONVERSION CHART
One Standard Drink Is Equal To

◆ **12 oz of BEER (5%)**

◆ **5 oz of WINE (10% – 12%)**

◆ **3 oz of FORTIFIED WINE (16% – 18%)**

◆ **1.5 oz of HARD LIQUOR (86 proof – 100 proof; 43% – 50%)**

◆ WINE: 1 Bottle

25 oz/750 ml	=	5 standard drinks
40 oz/1.5 liter	=	8 standard drinks
25 oz fortified	=	8 1/3 standard drinks

◆ HARD LIQUOR: 1 Bottle

12 oz (mickey)	=	8 standard drinks
26 oz	=	17 1/3 standard drinks
40 oz	=	26 2/3 standard drinks