16.1.9 Documentation of Statistical Methods

This section contains the following documents:

Statistical analysis plan version 3.0 dated 01 June 2017

Statistical analysis plan addendum version 2.0 dated 26 January 2018

Galectin Therapeutics Inc

GT-026

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

1June2017

Statistical Analysis Plan

Version 3.0

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Upon review of this document, the undersigned approves the statistical analysis plan. The analysis methods are acceptable, and the table, listing, and figure shell production can begin.

Author: Shelley Liu, Sr. Biostatistician, I am the author of this document, 20 Jul 2017 09:22:51 -04:00 GMT Date: _____

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Galectin Reviewer
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Version	Date	Brief description of changes	By whom
1.0	30MAR2015	Original	Yu Feng
2.0	02JUN2015	Updated based on protocol amendment	Yu Feng
3.0	JUNE2017	Updated based on new request on topline analysis	Shelley Liu

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List of Abbreviations

Abbreviation	Definition
α-SMA	Alpha smooth muscle actin
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUDIT	Alcohol Use Disorders Identification Test
BLQ	Below the limit of quantitation
BMI	Body mass index
CI	Confidence interval
CLDQ	chronic liver disease questionnaire
C_{max}	Observed maximum plasma or serum concentration after administration
CPA	Collagen proportional area
CV	Coefficient of variation
cPDR	Percentage dose recovery
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
FHVP	Free hepatic venous pressure
GEE	Generalized estimating equation
GR-MD-02	Galactoarabino-rhamnogalaturonate
HRQOL	Health-related quality of life
HVPG	Hepatic venous pressure gradient
IMP	Investigational medicinal product
IWRS	Interactive web response system
LBM	Lean body mass
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MELD	Model for End-stage Liver Disease
MITT	Modified-intent-to-treat
MMRM	Mixed Model Repeated Measures
NASH	Nonalcoholic steatohepatitis
OLES	Open-label extension study
PK	Pharmacokinetic(s)
PP	Per-protocol set
PPD	Pharmaceutical Product Development
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal value
WHO	World Health Organization
WHVP	Wedged hepatic venous pressure

1. Introduction

Nonalcoholic steatohepatitis (NASH) is liver inflammation and damage caused by a buildup of fat in the liver which is becoming common in the United States. It develops most often in patients with at least one of the following risk factors: obesity, dyslipidemia, and glucose intolerance. Cirrhosis with portal hypertension due to NASH will eventually lead to liver transplantation or death.

Galectin-3 protein has recently been implicated in the pathogenesis of NASH. Galactoarabino-rhamnogalacturonate (GR-MD-02) has been shown to be safe and well tolerated at single and multiple doses of 2, 4, and 8 mg/kg in a Phase 1 study (Galectin 2014). 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 Phase 2 dosing regimen.

The purpose of the Statistical Analysis Plan (SAP) is to describe the analyses and data presentations for Galectin's protocol GT-026. This SAP outlines the types of analyses that will address the study objectives, and explains in detail how the data will be handled and analyzed. It contains the definitions of analysis populations and statistical methods for the analysis of efficacy, safety and PK.

2. Objectives

2.1. Primary Objective

The primary objective of this study 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:

- 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 change in Ishak histopathological staging at 1 year compared to placebo as assessed on liver biopsy
- The effect of GR-MD-02 on liver stiffness as determined by the FibroScan® score (for those study centers where the FibroScan® is available) prior to the first infusion, at Infusion Visit 13, and 14 to 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 percentage dose recovery ($cPDR_{30}$) 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 to 28 days after final infusion as compared to placebo

- The effect of GR-MD-02 on change in Brunt-Kleiner histopathological staging at 1 year compared to placebo as assessed on liver biopsy
- 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 shall include the presence of lethargy, disorientation, inappropriate behavior, and the presence of asterixis)
    - an increase from baseline in Child-Turcotte-Pugh Score ≥2 points
    - 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 of this study are to evaluate:

- Difference in health-related quality of life (HRQOL) 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 to 28 days after final infusion
- Changes in liver biopsy staining for alpha smooth muscle actin (α-SMA) and galectin-3 in subjects treated with GR-MD-02 or placebo at 1 year

2.4. Safety Objectives

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

2.5. Pharmacokinetic Objective

The PK objectives are to evaluate systemic exposure following multiple doses of GR-MD-02 and to explore the population pharmacokinetics of GR-MD-02 in subjects with NASH with portal hypertension and cirrhosis.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 2, multi-center, parallel group, North American, randomized, placebo-controlled, double-blind study of subjects with portal hypertension due to cirrhosis.

Approximately 156 subjects with portal hypertension (HVPG ≥6 mm Hg) will be enrolled in the study at 45 to 60 study centers in the US and Canada. The subject must have a liver biopsy showing cirrhosis (Ishak stage 5 or 6) 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 randomized in a 1:1:1 ratio according to the randomization schedule to receive 1 of 3 treatment assignments: placebo, GR-MD-02 in dose of 2 mg/kg lean body mass (LBM), or GR-MD-02 in a dose of 8 mg/kg LBM administered every other week over a 52 week period for a total of 26 infusions. (Figure 3-1)

The study includes Prescreening, Screening, Treatment, Follow-up phases.

Prescreening: Prescreening may begin at Week -9 to evaluate the eligibility for diagnosis of NASH and FibroScan® (at sites where it is available). Subjects with qualifying diagnosis and FibroScan® score may proceed to screening.

Screening: The screening window is up to 8 weeks after prescreening visit. Subjects will undergo the following required procedures to assess eligibility during the screening period: EGD, HVPG measurement, liver biopsy, MBT (if available) and serum transaminases. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will proceed to randomization and the treatment phase.

Treatment Phase: Subjects will be randomly assigned (1:1:1) to receive 1 of 3 treatment assignments before the first infusion and will be administered every other week over a 52 week period for a total of 26 infusions. Safety and efficacy assessment will be monitored during the treatment phase.

Medical Care of Cirrhosis During the Study: General care of subjects with cirrhosis will be maintained during the study, including screening for hepatocellular carcinoma, at the discretion of the investigator.

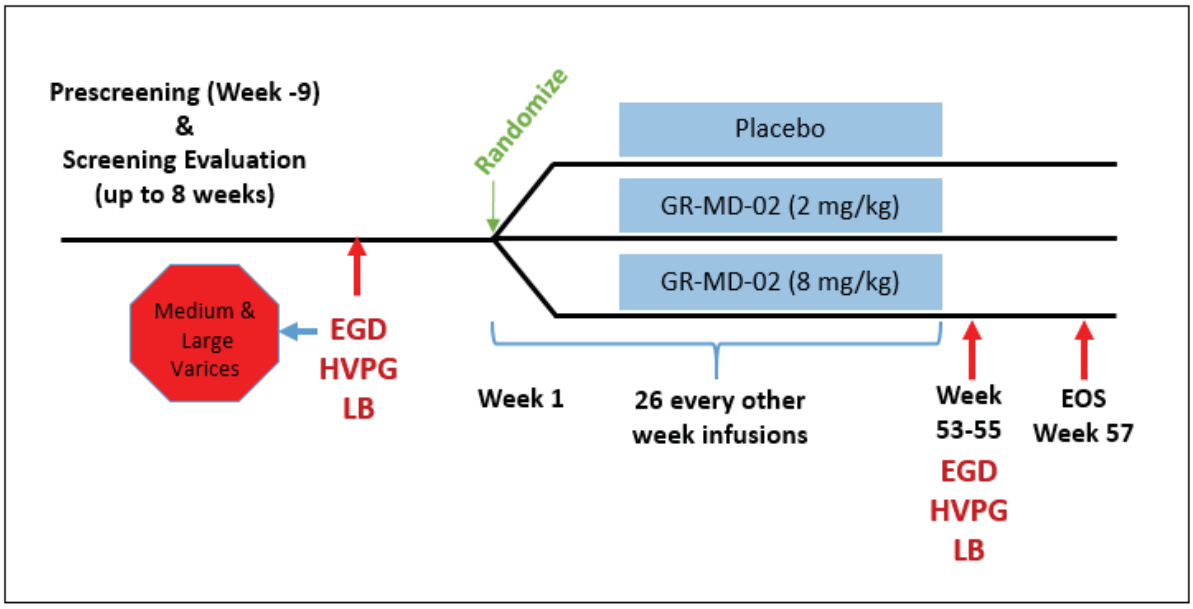
Post Final Visit (14-28 Days): All subjects will attend a visit (or visits) 14 to 28 days after final dose. During this visit, selected safety and efficacy assessments will be collected/performed.

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, safety assessments will be collected/performed. Whenever possible, all subjects who are terminated from the study early should have a FibroScan® and an MBT performed at a follow-up visit. Whenever possible, subjects who are terminated from the study following at least 13 infusions should also have all the post-study evaluations including EGD, HVPG, and liver biopsy performed in addition to the FibroScan® and MBT.

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 phone 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 liver transplantation, liver transplantation, or complications of chronic liver disease (ascites, spontaneous bacterial peritonitis, variceal bleeding, and encephalopathy).

Figure 3-1 Study Design GT-026



3.2. Study Endpoints

3.2.1. Primary Endpoint

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 or 8 mg/kg).

3.2.2. Secondary Endpoints

- The baseline-adjusted mean change in the CPA at 1 year as determined by digital morphometric analysis of liver biopsies
- Proportion of subjects who have at least one stage change in Ishak histopathological staging of fibrosis at 1 year as assessed on liver biopsy
- The baseline-adjusted mean change in liver stiffness as determined by FibroScan® (if available) score prior to the first infusion, at Infusion Visit 13, and 14 to 28 days after final infusion
- The baseline-adjusted mean 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 to 28 days after final infusion
- Proportion of subjects who have at least one stage change in Brunt-Kleiner histopathological staging of fibrosis at 1 year as assessed on liver biopsy

- 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 from baseline in Child-Turcotte-Pugh Score ≥2 points
  - 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

3.2.3. Exploratory Endpoints

- 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 to 28 days after final infusion
- Changes in liver biopsy staining for α-SMA and galectin-3 in subjects treated with GR-MD-02 or placebo at 1 year

3.2.4. 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.

3.2.5. PK Endpoint

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

The population PK analysis will be described in a separate modeling analysis plan.

4. General Statistical Considerations

Study day for events on or after the date of the first infusion will be defined as the number of days from the date of the first infusion of IMP, plus 1 day, so that the date of the first

infusion will be defined as Day 1. For events before the date of the first infusion, study day will be calculated as the difference in days between the date of the first infusion and the date of interest. Thus, the day before the date of the first infusion will be defined as Day -1. This means there will be no study day zero (0).

Baseline is defined as the last assessment prior to the first infusion of IMP. All baseline measurements must have been collected prior to administration of first infusion of IMP. Measurements that are obtained after the first infusion of IMP will be considered as post-baseline values. If the measurement of a variable is not made on a given subject prior to the first infusion of IMP, then that subject will be considered not to have a baseline value for that variable. Change from baseline is defined as post-baseline assessment minus baseline assessment.

Continuous data will be described using the following descriptive statistics: the number of subjects (n), mean, standard deviation (SD), median, the first quartile (Q1), the third quartile (Q3), minimum and maximum, where appropriate. Categorical data will be summarized using the frequency count (n) and percentage (%) of subjects for each category, where appropriate.

Unless otherwise specified, all statistical tests and confident intervals (CIs) will be two-sided and conducted at the 0.05 significance level. If analysis variables are not normally distributed, Poisson-regression model (or the negative binomial) will be applied for counts data.

No imputation will be applied for missing data unless otherwise specified.

All collected data used for safety and efficacy evaluations will be presented in listings. Data will be displayed in all listings sorted by treatment group and subject identifier unless specified otherwise.

All analyses will be conducted using SAS® Version 9.1.3 or higher. The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding adverse events. Prior or concomitant medication data will be coded using the World Health Organization (WHO) Drug Dictionary.

4.1. Sample Size

The sample size of 52 subjects per treatment arm assumes a mean difference in the change of HVPG from baseline at 52 weeks between an active treatment arm and placebo of 2 mm Hg with a SD of 3 mm Hg, and allows for a 25% dropout rate and 80% power to detect a statistically significant difference at an α level of 0.05. A difference of 2 mm Hg in the change of HVPG is considered to be of “clinical significance” (Villanueva 2009; Escorsell 2000; Abraldes 2003). The SD of 3 mm Hg at a mean change of HVPG of 2 mm Hg from baseline is based on primary data, obtained from an investigator (Dr Guadalupe Garcia-Tsao), as reported in a published longitudinal clinical study (Groszmann 2005).

4.2. Randomization, Stratification, and Blinding

Approximately 156 eligible subjects will be randomly assigned to one of the following 3 treatment groups in a 1:1:1 ratio:

- Approximately 52 subjects are assigned to GR-MD-02 in dose of 2 mg/kg LBM
- Approximately 52 subjects are assigned to GR-MD-02 in dose of 8 mg/kg LBM
- Approximately 52 subjects are assigned to placebo

The randomization mechanism for the study will be deployed within an interactive web response system (IWRS). Unblinded biostatisticians will generate the randomization schedule using SAS software Version 9.2 or later for IWRS which will link sequential subject randomization numbers to treatment codes allocated at random with a 1:1:1 randomization ratio.

Except in an emergency, investigators, Galectin, or other persons involved in study conduct will not know the randomization schedule and study drug allocation before study completion. The IWRS system will be used if emergency unblinding is required. This would generally only be used in an emergency, when knowledge of the actual treatment becomes medically necessary.

4.3. Analysis Set

4.3.1. Full-Analysis Set

The full-analysis set (FAS), or intent-to-treat group, will consist of all subjects who were randomly assigned to IMP. The FAS will be used as the primary efficacy analysis set.

All subjects in the FAS set will be analyzed according to the treatment they were randomized to receive.

4.3.2. Modified-Intent-to-Treat Set

The Modified-Intent-to-Treat (MITT) set will consist of all subjects who were randomly assigned, received at least 1 infusion, and had at least 1 post-baseline efficacy assessment.

All subjects in the MITT set will be analyzed according to the treatment they were randomized to receive.

4.3.3. Per Protocol Set

The per protocol (PP) 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 subjects in the PP set will be analyzed according to the treatment they actually received.

4.3.4. Safety Set

The safety set will consist of all subjects who received any IMP. All subjects in the safety set will be analyzed according to the treatment they actually received.

4.3.5. Pharmacokinetic Set

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

5. Subject Disposition

5.1. Disposition

A disposition of subjects includes the number and percentage of subjects for the following categories: subjects who were randomized, subjects who completed the study, subjects who discontinued from the study. All percentages will be based on the number of subjects randomized using the FAS population.

The reasons for discontinuation of study participation will also be summarized in the tables.

Subject disposition data will be presented in a listing.

5.2. Protocol Deviations

Protocol deviations/violations will be identified and assessed by the investigator in accordance with the procedures or processes approved by the sponsor. The protocol deviations/violations will be defined prior to unblinding of the database. The significant protocol deviations/violations will be summarized by treatment group using the FAS population. A listing of subjects with all protocol deviations/violations will also be provided.

6. Demographics and Baseline Characteristics

This summarization will be based on the FAS population set and presented by treatment group and overall. Descriptive statistics will be calculated for continuous variables and frequency counts and percentages will be applied to categorical variables. No inferential statistics will be presented. All subject demographic and baseline characteristic data will be presented in listings.

6.1. Demographics

The demographics and baseline characteristics summary will be presented in a table by treatment group and overall. The following variables will be included:

- Age (years)
- Sex (male, female)
- Race

- Ethnicity
- Baseline height (cm)
- Baseline weight (kg)
- Baseline body mass index (BMI) (kg/m^2)
- Baseline lean body mass (LBM) (kg)
- Baseline Alcohol Use Disorders Identification Test (AUDIT)

Age in years will be calculated by using the date of birth from the informed consent date and will be rounded down to an integer. BMI is calculated as follows:

$$BMI = \text{weight (kg)} / (\text{height (m)})^2$$

Alcohol consumption will be evaluated by AUDIT which contains 10 questions scaling from 0 to 4, the total score based on the sum of 10 individual scores will be summarized.

6.2. Baseline Disease Characteristics

Summaries of baseline disease characteristics will be presented by treatment group and overall, and include, but are not limit to the baseline HVPG, diagnosis of NASH, CPA, FibroScan® (if available) score, Ishak histopathological stage and Brunt-Kleiner histopathological stage.

6.3. Alcohol Usage

Alcohol timeline followback (TLFB) will be used to assess subjects' alcohol consumption for the years 2015, 2016 and 2017. Subjects' daily drinking will be recorded as amount of standard drink on the calendar. The estimate daily drinking over the time will be summarized by treatment group and overall for the FAS population.

6.4. Medical and Surgical History

The number and percentage of subjects with any medical and surgical history will be summarized overall and for each body system. Body systems will be included as recorded on the eCRF. Percentages will be calculated based on number of subjects for the safety population.

Subject medical history data including specific details will be presented in a listing.

6.5. Inclusion and Exclusion Criteria

Subjects who do not meet all inclusion and exclusion criteria, as presented in Section 4.1.1 and 4.1.2 of the protocol, will be presented in a listing.

7. Treatments and Medications

This summarization of treatments and medications will be based on the safety population set and presented by treatment group and overall. Descriptive statistics will be calculated

for continuous variables and frequency counts and percentages will be applied to categorical variables. No inferential statistics will be presented.

7.1. Prior and Concomitant Medications

All prior medications for liver cirrhosis and NASH will be recorded in the eCRF and all other 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. A concomitant medication is defined as medications taken any time after the first infusion of IMP. A prior medication is defined as nonstudy medications discontinued prior to the first infusion of IMP.

Missing start dates for concomitant medications data will be handled as follows (where UK, UKN and UKNW indicate unknown or missing Day, Month and Year respectively):

- UK-MMM-YYYY: impute 01-MMM-YYYY. If the month and year are the same as the first dose month and year, then impute the date of the first dose;
- UK-UKN-YYYY: If the year is prior to the year of the first dose, impute 01-JAN-YYYY of the collected year. If the year is the same as the first dose year, then impute the date of the first dose. If the year is after the year of the first dose, impute 01-JAN-YYYY;
- UK-UKN-UKNW: impute date of the first dose.

Missing stop dates for concomitant medications data will be handled as follows (where UK, UKN and UKNW indicate unknown or missing Day, Month and Year respectively):

- UK-MMM-YYYY: impute the last day of the month;
- UK-UKN-YYYY: impute 31-DEC-YYYY;
- UK-UKN-UKNW: leave as missing.

If imputed start date is after the end date of concomitant medication, the start date will be set same as end date.

Prior and concomitant medications will be coded using the World Health Organization Drug dictionary (WHO Drug) Version 1 March 2015. The dictionary will be updated throughout the life of the project to allow for the most recent version of the dictionary to be used. The medication names will be coded according to the Anatomical Therapeutic Chemical (ATC) class and preferred terms provided in the dictionary.

Prior and concomitant medications will be summarized in separate tables. The tables will present the number and percentage of subjects by ATC class and preferred term for each treatment group and overall. ATC classes will be sorted in decreasing order of frequency based on the total number of subjects who take each medication in the total column, while preferred terms within each drug class will be presented alphabetically. In addition, the total number of medications and the number and percentage of subjects receiving at least 1

medication will also be presented. If a subject has multiple medications for a given preferred term the subject will only be counted once.

All prior and concomitant medications will be presented in a listing.

7.2. Study Treatments

GR-MD-02 and matching placebo will be available in 10-mL sterile vials at a concentration of 30 mg/mL. The treatment regimen consists of 26 injection visits biweekly from week 1. The dosing will be determined by LBM, since it is anticipated that many subjects will be obese and GR-MD-02 is distributed primarily in the blood compartment.

7.2.1. Extent of Exposure

Duration of exposure is defined as the total number of days a subject is exposed to study medication and will be presented as the total number of days from the first infusion date to the last infusion date (date of last infusion minus the date of first infusion + 1).

The exposure to study drug is defined as the cumulative number of injections taken by subjects, since dose is based on subjects' LBM.

The extent of exposure and study drug exposure will be summarized descriptively in a table.

A listing will present subject data for first dose date, last dose date, extent of exposure, and study drug exposure.

7.2.2. Treatment Compliance and Modifications

Treatment compliance is defined as

$$\text{Compliance (\%)} = \frac{\left(Number\ \ of\ injections\ \ \ received\ \right)\times 100}{Number\ \ of\ injections\ \ \ planned\ \ \ to\ be\ received\ \ \ during\ \ \ the\ study}$$

The overall study drug compliance rate will be summarized by treatment group using the descriptive statistics. The number and percentage of subjects in each of the following compliance rate categories (<80, >=80 to 100) will also be reported.

Percentages will be calculated out of the number of subjects who were dosed at that dosing period. The number and percentage of subjects in each compliance rate category will be presented.

8. Efficacy Analysis

All efficacy analyses will be performed using the FAS population. Specific analyses, detailed below, will be performed on the MITT and the PP populations.

8.1. Primary Efficacy Endpoint

HVPG will be collected at screening and 14 to 28 days after final dose (53-55 weeks), and used as a measure of portal hypertension. Both wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) will be measured for subjects without varices or with small varices. HVPG is defined as the difference between the WHVP and the FHVP. A single experienced investigator, Dr Guadalupe Garcia-Tsao (Yale University), will evaluate all HVPG tracings at a central reading facility.

The HVPG will be summarized for the FAS population by visit and treatment group, for all scheduled visits, along with the change from baseline descriptively in a summary table and graphically. In addition, the number and percentage of subjects will be summarized by the following HVPG categories (mild portal hypertension (MPH) ie ≥6 mmHg to <10 mmHg and clinically significant portal hypertension (CSPH) ie ≥10 mmHg).

8.1.1. Primary Analysis

The primary efficacy endpoint, change from baseline in HVPG at 1 year (53 to 55 weeks), will be analyzed using analysis of covariance (ANCOVA) with baseline values taken as a covariate using the FAS population at a significant level of 0.05 (2-sided). Treatment effect will be evaluated as a contrast of each active treatment versus placebo and described using continuous summary. To control the type I error rate due to multiple comparisons, the Bonferoni-Holm (1988) procedure for the comparison between treatment group and control will be implemented. Estimate of mean difference along with 95% CI will also be presented.

Missing HVPG at 1 year will be imputed using the last observation carried forward (LOCF) method. The sensitivity analysis will be performed on the change from baseline in HVPG based on the LOCF values in the FAS population using the same statistical methodology described above.

Additional sensitivity analyses for HVPG will include:

- Change from baseline in HVPG at 1 year in the MITT population.
- Change from baseline in HVPG at 1 year in the PP population.

The following subgroup analysis will also be conducted in the MITT population:

- Change from baseline in HVPG at 1 year by baseline HVPG category of MPH and CSPH
- Change from baseline in HVPG at 1 year by gender.
- Percentage of subjects who have ≥ 10% and ≥ 20% decrease at 1 Year in HVPG by baseline HVPG category of MPH and CSPH
- Percentage of subjects with HVPG at CSPH level at Baseline and at MPH level at 1 Year

8.2. Key Secondary Efficacy Endpoints

There are six key secondary efficacy endpoints: CPA, Ishak histopathological stage, FibroScan®, MBT, Brunt-Kleiner histopathological stage and complications of cirrhosis.

CPA

CPA will be used to measure liver collagen (a surrogate for fibrosis) by evaluation of liver biopsy at screening and 14 to 28 days after final dose (53 to 55 weeks). A single experienced pathologist, Dr Zack Goodman (INNOVA Medical Center), will evaluate all liver biopsies at a central pathology laboratory.

The CPA will be summarized for the FAS population by visit and treatment group, for all scheduled visits, along with the change from baseline descriptively in a summary table and graphically.

Ishak histopathological stage

Fibrosis will be evaluated by liver biopsy and be staged according to the Ishak histopathological stage (0-6) at screening and 14 to 28 days after final dose (53 to 55 weeks).The number and percentage of subjects by Ishak histopathological stage will be summarized using the FAS population by treatment group. The number and percentage of subjects changing in Ishak histopathological stages will also be presented.

FibroScan®

FibroScan® will be only performed at the study centers where it is available and used to evaluate liver stiffness which is recorded as the pressure measurement of kPa at the scheduled visits.

The FibroScan® (if available) will be summarized for the FAS population by visit and treatment group, for all scheduled visits, along with the change from baseline descriptively in a summary table and graphically.

MBT

The MBT will only be performed at the study centers where it is approved. The cumulative percentage dose recovery of the metabolized ^{13}C-methacetin 30 minutes after ingestion of the test substrate will be used as the MBT parameter for this study. Delta over baseline (DOB) with corresponding time point (T_n) will be collected on the eCRF.

The cPDR$_{30}$ is defined as:

$$cPDR_{30} = \frac{\frac{T_1}{60} \bullet PDR_1}{2} + \sum_{i=2}^{n} \frac{\frac{T_i - T_{i-1}}{60} \bullet \left(PDR_i + PDR_{i-1}\right)}{2}$$

where $PDR_i = 1.817853 \times DOB_i \times w^{0.5378} \times h^{0.3963}$, $w = weight$ (kg), $h = height$ (cm).

Brunt-Kleiner histopathological stage

Fibrosis will be evaluated by liver biopsy and be staged according to the Brunt-Kleiner histopathological stage (0-4) at screening and 14 to 28 days after final dose (53 to 55 weeks).

The number and percentage of subjects by Brunt-Kleiner histopathological stage will be summarized using the FAS population by treatment group. The number and percentage of subjects changing in Brunt-Kleiner histopathological stages will also be presented.

Complications of cirrhosis

Complications of cirrhosis with portal hypertension is 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 points
- 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

The incidence of complications will be summarized in a table with count and percentage of subjects by each complication event using the FAS population by treatment group. Subjects with any complication event will also be presented.

In addition, Child-Turcotte-Pugh score and MELD score will be summarized descriptively at the scheduled visits. Child-Turcotte-Pugh class and MELD score (<15, ≥15) will also be summarized.

8.2.1. Key Secondary Efficacy Analysis

The 6 key secondary efficacy endpoints will be examined using a gatekeeper statistical approach and will be tested sequentially in the order of 1) CPA, 2) FibroScan®, 3) Ishak histopathological stage, 4) MBT, 5) Brunt-Kleiner histopathological stage, 6) complications of cirrhosis. Analysis of the secondary endpoints will be conducted if the primary endpoint is significant ($\alpha<0.05$). If a secondary endpoint does not meet statistical significance, then all the subsequent secondary endpoints will be treated as exploratory.

CPA

The change from baseline in CPA at 1 year (53 to 55 weeks), will be analyzed using robust regression (M estimation method, Huber 1973) using the FAS population at a significant level of 0.05 (2-sided). Treatment effect will be evaluated as a contrast of each active treatment versus placebo and described using continuous summary.

Sensitivity analyses for CPA will include:

- Change from baseline in CPA at 1 year will be analyzed based on the LOCF values using the FAS population.
- Change from baseline in CPA at 1 year will be analyzed using the MITT population.
- Change from baseline in CPA at 1 year will be analyzed using the PP population.

Ishak histopathological stage

The proportion of subjects who have at least one stage change in Ishak histopathological staging of fibrosis at 1 year will be analyzed using the FAS population. Fisher Exact Test will be used to compare the difference between treatment groups.

Sensitivity analyses for Ishak histopathological stage will include:

- The proportion of subjects who have at least one stage change in Ishak histopathological staging of fibrosis at 1 year will be analyzed using the MITT population.
- The proportion of subjects who have at least one stage change in Ishak histopathological staging of fibrosis at 1 year will be analyzed using the PP population.

FibroScan®

The change from baseline in FibroScan® (if available) at 1 year will be analogous to the primary efficacy endpoint, using the ANCOVA model for the FAS population. The baseline value of FibroScan® (if available) will be used as a continuous covariate in the ANCOVA model.

Sensitivity analyses for FibroScan® (if available) will include:

- Change from baseline in FibroScan® (if available) at 1 year will be analyzed based on the LOCF values using the FAS population.
- Change from baseline in FibroScan® (if available) at 1 year will be analyzed using the MITT population.
- Change from baseline in FibroScan® (if available) at 1 year will be analyzed using the PP population.
- Treatment effect for FibroScan® (if available) overtime will be estimated using a mixed model repeated measures (MMRM) analysis with the FAS population.

MBT

The change from baseline in MBT (if available) at 1 year will be analogous to the primary efficacy endpoint, using the ANCOVA model using the FAS population. The baseline MBT will be used as a continuous covariate in the ANCOVA model.

Sensitivity analyses for MBT (if available) will include:

- Change from baseline in MBT (if available) at 1 year will be analyzed based on the LOCF values using the FAS population.
- Change from baseline in MBT (if available) at 1 year will be analyzed using the MITT population.
- Change from baseline in MBT (if available) at 1 year will be analyzed using the PP population.
- Treatment effect for MBT (if available) overtime will be estimated using MMRM analysis with the FAS population.

Brunt-Kleiner histopathological stage

The proportion of subjects who have at least one stage change in Brunt-Kleiner histopathological staging of fibrosis at 1 year will be analyzed using the FAS population. Fisher Exact Test will be used to compare the difference between treatment groups.

Sensitivity analyses for Brunt-Kleiner histopathological stage will include:

- The proportion of subjects who have at least one stage change in Brunt-Kleiner histopathological staging of fibrosis at 1 year will be analyzed using the MITT population.
- The proportion of subjects who have at least one stage change in Brunt-Kleiner histopathological staging of fibrosis at 1 year will be analyzed using the PP population.

Complications of cirrhosis

The incidence of complications of cirrhosis with portal hypertension at 1 year will be analyzed using the FAS population. A standard chi-square test will be used to compare the incidence of complications of cirrhosis between treatment groups.

Sensitivity analyses for complications of cirrhosis will include:

- The incidence of complications of cirrhosis with portal hypertension at 1 year will be analyzed using the MITT population.
- The incidence of complications of cirrhosis with portal hypertension at 1 year will be analyzed using the PP population.
- Time to complications of cirrhosis will be analyzed using Kaplan-Meier curves and compared between treatment groups using a log-rank test. Median time to

complications of cirrhosis, Q1 and Q3 will be presented, along with 95% CI. Time to complications of cirrhosis is defined as the time from the date of randomization to the first documentation of any complication of cirrhosis described in section 8.2. Subjects without development of complications of cirrhosis will be censored at the date of last assessment of cirrhosis complications.

8.3. Exploratory Endpoints

Each of the following exploratory efficacy endpoints will be analyzed analogous to the primary efficacy endpoint, using the ANCOVA model unless otherwise specified. For each endpoint, the baseline value of the endpoint will be used as a continuous covariate in the ANCOVA model.

- 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 α-SMA and galectin-3 in subjects treated with GR-MD-02 or placebo at 1 year will be evaluated using robust regression (M estimation method)

CLDQ

CLDQ is a self-administered questionnaire that consists 29 items on a seven-point scale, ranging from the worst (1) to the best (7) possible function. The questionnaire includes following 6 domains:

Domains	Items
Abdominal symptoms (AS)	1, 5, 17
Fatigue (FA)	2, 4, 8, 11, 13
Systemic symptoms (SS)	3, 6, 21, 23, 27
Activity (AC)	7, 9, 14
Emotional function (EF)	10, 12, 15, 16, 19, 20, 24, 26
Worry (WO)	18, 22, 25, 28, 29

Average score of each domain will be computed. The average score across six domain average scores will also be derived as the overall average score. The derived domain average and overall average score will be summarized at scheduled visits. If the score is missing for some individual items, the domain average score should be calculated as an average of available items if more than 50% of items in that domain are available. If 50% or less of the items are available for a domain, the domain average score is set as missing too.

FibroTest (FibroSure) and ELF Score

Missing values will be imputed using the LOCF method for the post-baseline visits for FibroTest score and ELF score. Also, the ANCOVA model will be conducted for both observed values and LOCF values.

Treatment effects for FibroTest score and ELF score overtime will be estimated using MMRM analysis with the FAS population respectively.

Each exploratory test will also be summarized for the FAS population at all scheduled visits, along with the change from baseline descriptively in summary tables.

9. Safety Analysis

All analysis of safety will be conducted using the Safety set.

9.1. Adverse Events

An adverse event (AE), including serious AE (SAE), is defined as any untoward medical occurrence in a subject enrolled into this study, regardless of its causal relationship to IMP.

A treatment-emergent adverse event (TEAE) is defined as any event which occurs on or after the first double-blind dose date and up to 30 days after the last dose date of the double-blind study drug.

In order to determine a TEAE when the start date of an AE is missing or incomplete, it will be assumed to have occurred after the first infusion of IMP except if an incomplete date indicates that the event started prior to the first infusion.

In the event that only a partial end date (month/year) is available, and the month/year occurs before Day 1 of the study, the AE will not be considered treatment-emergent. However, the partial onset date (month/year) of AE will be handled as follows (where UK, UKN and UKNW indicate unknown or missing Day, Month and Year respectively):

- UK-MMM-YYYY:
    - impute the last day of the month, if the year is less than the first dose year or the year is the same as the first dose year and the month is less than or equal to the first dose month;
    - impute 01-MMM-YYYY, if the year is greater than the first dose year or the year is the same as the first dose year and the month is greater than the first dose month;
    - impute the date of the first dose, if the month and year are the same as the first dose month and year.
- UK-UKN-YYYY:
    - impute 31-DEC-YYYY, if the year is less than the first dose year;

  - impute 01-JAN-YYYY, if the year is greater than the first dose year;
  - impute the date of the first dose, if the year are the same as the first dose year.
- UK-UKN-UKNW: impute date of the first dose.

If the AE end date is complete and the partial AE start date imputed by the rules above is after the AE end date, then the start date will be imputed by the AE end date.

All AEs will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0. Severity of AE will also be reported according to the NCI Common Terminology Criteria for Adverse Events version 4.03.

The incidence of AEs will be summarized in tables with count and percentage of subjects with AEs by system organ class (SOC) and preferred term. Unless otherwise specified, at each level of SOC or preferred term, a subject with multiple events will only be counted once per SOC or preferred term. Percentages of subjects with AEs will be calculated out of the number of subjects in the safety population. Tables will be sorted by SOC and preferred term based on total frequency in overall group.

The following categories of AE will be summarized:

- TEAEs
- Severity (1, 2, 3, 4 and 5) of AEs
- Relationship of AEs to study drug
- Grade 3 or greater AEs
- AEs leading to discontinuation of study treatment
- AEs leading to death
- Relationship of TEAEs to study drug
- Grade 3 or greater TEAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to death
- SAEs
- Serious TEAEs
- Serious and grade 3 or greater TEAEs
- Serious TEAEs leading to discontinuation of study treatment
- Serious TEAEs leading to death

All AEs will be presented in data listings. TEAEs will be flagged in the listings.

9.1.1. Relationship of Adverse Events to Study Drug

The relationship of AEs to study drug (Unrelated, Possible, Probable, Definite) will be summarized. Possible, probable, definite will be considered as related to study drug. If relationship to treatment is missing, it will be assumed to be related.

9.1.2. Severity of Adverse Events

All AEs will be summarized by maximum severity (1, 2, 3, 4 and 5). If a subject reports multiple occurrences of a specific event within a specific analysis period, the subject will be counted only once by the maximum severity. No imputation will be done for missing severity.

9.2. Clinical Laboratory Evaluations

Laboratory assessments, including hematology, coagulation and chemistry, will be evaluated over time on the study. All summaries will be based on the units provided by the central laboratory, no conversion will be done and missing values will not be imputed. Urinalysis assessments will only be collected at screening visit.

Summary statistics of the observed values and change from baseline will be provided at the scheduled visits for hematology, coagulation and chemistry laboratory parameters. The number and percentage of subjects with shift in normal/abnormal from baseline will be presented in a shift table at the post-baseline scheduled visits for hematology, coagulation and chemistry laboratory parameters.

Clinically significant laboratory values will be summarized for subjects meeting at least one of the criteria and change from baseline will be presented in a shift table.

- Alanine aminotransferase (ALT) ≥3 × Upper Limit of Normal Value (ULN) and total bilirubin ≥2 × ULN
- Aspartate aminotransferase (AST) ≥3 × ULN and total bilirubin ≥2 × ULN
- Albumin <2.8 g/dL

All laboratory data will also be presented in listings.

9.3. Biomarker Measurements

A blood sample will be collected for assessment of galectin-3 at Infusion Visits 1, 7, 13, 20, and 14 to 28 days after final infusion. Summary statistics of the observed values and change from baseline will be provided at the scheduled visits for the safety population.

9.4. Vital Sign Measurements

Vital sign measurements including respiratory rate (bpm), heart rate (beats per minute), temperature (C), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), weight (kg) and BMI (kg/m^2) will be summarized descriptively using the safety population

at the scheduled visits. Change from baseline values will also be summarized descriptively at the scheduled visits. All vital signs will be presented in a listing.

9.5. Physical Examination

A complete physical examination will be performed at screening, with particular attention to examination for stigmata of liver disease/cirrhosis. A limited physical examination will only include weight and examination of the heart, lung, and abdomen during the treatment phase.

The number and percentage of subjects with each physical examination outcome (normal, abnormal, or not done) will be summarized using the safety population by body system at scheduled visits. Also the number and percentage of subjects with change from baseline will be presented in a shift table by body system at the post-baseline scheduled visits.

All physical examination results will be presented in a listing.

9.6. Electrocardiogram (ECG)

12-lead ECG assessments including PR interval (milliseconds), QRS interval (milliseconds), QT interval (milliseconds), and QTc interval (milliseconds) will be summarized descriptively using the safety population at the scheduled visits. Change from baseline values will also be summarized descriptively at the scheduled visits,

The number and percentage for ECG overall interpretation (normal or abnormal and not clinically significant vs. clinically significant,) will be summarized at scheduled visits. Also the number and percentage of subjects with change from baseline will be presented in a shift table at the post-baseline scheduled visits.

All ECG assessments will be presented in a listing.

10. Pharmacokinetics

All PK analysis will be conducted using the PK population.

10.1. Plasma Concentrations

PK blood samples will be collected at the following times:

- Infusion Visit 1: Approximately 2 hours following the end of the infusion, on the day following the infusion (Nondosing Visit 1 [ie, Day 2]), and on Nondosing Visit 2 (ie, Day 3) following the infusion. The blood sample collections on Nondosing Visits 1 and 2 (ie, Days 2 and 3) can occur at any time during those days.
- Infusion Visit 2: Approximately 2 hours following the end of the infusion
- Infusion Visit 3: Approximately 2 hours following the end of the infusion
- Infusion Visit 4: Approximately 2 hours following the end of the infusion and on Nondosing Visit 3 (which can be either Day 2 or 3 following the infusion). The

blood sample collection on Nondosing Visit 3 (ie, Day 2 or 3) can occur at any time during those days.

- Infusion Visit 7: Any time after the end of infusion on the day of the infusion.

The individual plasma concentrations of GR-MD-02 will be listed for each subject. The listing will include subject number, dose group, scheduled visit, date and time of collection, actual relative time to dose, and plasma concentrations. All concentrations below the limit of quantification (BLQ) or missing data will be labelled as such in concentration data listings.

GR-MD-02 concentrations will be summarized using descriptive statistics by dose group, visit, and scheduled time point. Descriptive statistics will include arithmetic mean, SD, coefficient of variation (CV), minimum, median, maximum, geometric mean and geometric mean CV. Concentrations that are BLQ will be treated as zero in the summary statistics of concentration data. All missing concentrations will be treated as missing in the summary statistics of concentration data.

Plots of arithmetic mean (±SD) concentration versus visit and time (both linear and semi-logarithmic) by dose group and individual concentrations versus visit and time (both linear and semi-logarithmic) will be provided. For ease of presentation, nominal sampling times will be used to present results in figures.

10.2. Plasma Pharmacokinetic Parameters

GR-MD-02 plasma concentrations will be used to evaluate systemic exposure following multiple dosing. Based on the high correlation between the area under the concentration-time curve and C_{max} of GR-MD-02 in the Phase 1 clinical study (Galectin 2014) ($p<0.001$, r squared = 0.91), 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.

All PK analyses will be conducted by the Department of Clinical Pharmacology, PPD, Inc., Richmond, VA, USA.

11. Interim Analysis

An interim analysis of PK data is planned for the first Data Safety Monitoring Board (DSMB) meeting. It is expected that PK analysis will be performed on the GR-MD-02 plasma concentrations for the first 30 subjects after Infusion Visits 1, 2, 3, 4 and 7. There should be approximately 10 subjects who received 2 mg/kg and 10 subjects who received 8 mg/kg in this group of subjects.

12. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be composed of medical experts and an unblinded biostatistician who will not participate in the study. The DSMB will be responsible for periodically monitoring the safety of the clinical study and

providing recommendations for the study by reviewing the safety data 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.

The DSMB review will occur as follows:

- after the first 30 subjects in the study have received 7 doses of IMP;
- after the approximately 50% of subjects to be enrolled has received 13 doses of IMP;
- after 50% of subjects have received 26 doses of IMP.

In addition to review of the safety data, the first DSMB meeting will also assess GR-MD-02 C_{max} plasma levels after Infusion Visits 1, 2, 3, 4 and 7 for the first 30 subjects.

13. References

Galectin Pharmaceuticals, Inc. A Multi-Center, Partially Blinded, Maximum Tolerated Multiple Dose Escalation, Phase 1 Clinical Trial to Evaluate the Safety of GR-MD-02 in Subjects with Non-Alcoholic Steatohepatitis (NASH) with Advanced Hepatic Fibrosis. 17 Jun 2014. Protocol No. GT-020. Version 4. 96p.

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Galectin Therapeutics Inc

GT-026

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

26 Jan 2018

Statistical Analysis Plan Addendum

Version 2.0

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The additional data analysis as listed below will be performed as post-hoc analysis. The main objective is to repeat primary and secondary analysis on the following subgroups:

a. Patients with baseline (BL) varices, and patients without BL varices.
b. Patients with MPH (baseline HVPG 6 to <10 mmHg) and patients with CSPH (baseline HVPG (≥ 10 mmHg)

For definition of analysis set and other terminology or abbreviation, please refer to final SAP. However, the subject who was randomized but have not received any treatment will be removed from all analysis sets used in post-hoc. In addition, the missing value at scheduled visit will be imputed by result from subsequent unscheduled visit. For example, if a subject's HVPG at Week 53-55 visit was not collected, but there's a subsequent unscheduled visit with valid result, this unscheduled result will be used as subject's HVPG result at Week 53-55.

For LOCF analysis, include all patients that had an early termination visit, and carry forward their last observation result.

<u>Analyses on Primary Endpoint HVPG</u>

1. Perform ANCOVA to determine effect of varices on HVPG on FAS LOCF dataset:
    a. Week 53/55 HVPG is used as dependent with BL HVPG as covariate, and with dose, varices and dose varices interaction as fixed factors.
2. Run ANCOVA for FAS LOCF, mITT LOCF, and PP LOCF for HVPG with Least square difference (LSD) mean comparison (no Bonferroni correction) on subset of patients with / without baseline varices:
    a. BL Change in HVPG vs dose with BL HVPG as a covariate (i.e. adjust for baseline HVPG)
    b. Percent Change from BL HVPG vs dose with no covariate/no baseline adjustment
3. Perform similar ANCOVA/ANOVA analyses of MPH and CSPH for each subset, this would result in the following:
    a. Analyses of patients without varices and with MPH – using FAS LOCF, mITT LOCF and PP LOCF for HVPG with LSD mean comparison (no Bonferroni correction) on:
        i. ANCOVA for BL Change in HVPG vs dose with BL HVPG as a covariate (i.e. adjust for baseline HVPG)
        ii. ANOVA for Percent Change from BL HVPG vs dose with no covariate/no baseline adjustment
    b. Analyses of patients without varices and with CSPH - using ITT LOCF, mITT LOCF, and PP LOCF for HVPG with LSD mean comparison (no Bonferroni correction) on:
        i. ANCOVA for BL Change in HVPG vs dose with BL HVPG as a covariate (i.e. adjust for baseline HVPG)
        ii. ANOVA for Percent Change from BL HVPG vs dose with no covariate/no baseline adjustment

c. Analyses of patients with varices and with MPH (6 to <10 mmHg) -- using ITT LOCF LOCF, mITT LOCF and PP LOCF for HVPG with LSD mean comparison (no Bonferroni correction) on:
    i. ANCOVA for BL Change in HVPG vs dose with BL HVPG as a covariate (i.e. adjust for baseline HVPG)
    ii. ANOVA for Percent Change from BL HVPG vs dose with no covariate/no baseline adjustment
d. Analyses of patients with varices and CSPH (≥ 10 mmHg) -- using ITT LOCF, mITT LOCF, and PP LOCF for HVPG with LSD mean comparison (no Bonferroni correction) on:
    i. ANCOVA for BL Change in HVPG vs dose with BL HVPG as a covariate (i.e. adjust for baseline HVPG)
    ii. ANOVA for Percent Change from BL HVPG vs dose with no covariate/no baseline adjustment

<u>Analyses on Secondary Endpoint Collagen Proportional Area (CPA)</u>
All post-hoc analysis performed on HVPG parameter will be repeated for Collagen Proportional Area (CPA).

<u>Analyses on Secondary Endpoints using FAS set</u>

1. Perform BL Change vs. Dose using MMRM model for continuous data and Ordinal Logistic Regression (OLR) Analysis for categorical data for the following datasets: all data, With Varices, Without Varices, Without Varices and MPH, Without Varices and CSPH, With Varices and MPH, and With Varices and CSPH.
2. The change from baseline at Week 53/55 of categorical variable will be the response and treatment will be explanatory variable in OLR model. If Week 53/55 is missing, LOCF rule will be applied for imputation. The change from baseline will be classified to Decrease, No Change and Increase. The result of odds ratio and its 95%CI as well as p-value from Wald Chi Square test will be presented in the table. The lowest level ie Decrease is the event level in response.
3. The change from baseline at each visit of continuous variable will be the dependent variable in MMRM analysis. Baseline is the covariate and treatment, visit and interaction of treatment and visit are factors. If scheduled assessment is missing and a subsequent unscheduled assessment is available, the scheduled assessment will be imputed by unscheduled assessment.
4. The following parameters will be analyzed:
    a. Change in NAFLD Activity Score (OLR) (LVBNAS)
    b. Change in each Component of the NAFLD Activity Score:
        i. Change in hepatocyte ballooning score (OLR)
        ii. Change in inflammation (OLR)
        iii. Change in steatosis/fat (OLR)
    c. Change in Fibrosis Staging Score (OLR)

i. Ishak staging score (OLR)
ii. Brunt staging score (OLR)

d. Change in FibroTest Score (MMRM)
e. Change in each Component of the FibroTest Score:
    i. Change in Alpha2 Macroglobulin (MMRM)
    ii. Change in Haptoglobin (MMRM)
    iii. Change in Apolipoprotein A1 (MMRM)
    iv. Change in Gamma-glutamyl transpeptidase, GGT (MMRM)
    v. Change in Total Bilirubin (MMRM)
    vi. Change in Alanine Transaminase, ALT (MMRM)
f. Change in ELF Score (MMRM)
g. Change in each Component of the ELF Score:
    i. Change in tissue inhibitor of metalloproteinases 1, TIMP-1 (MMRM)
    ii. Change in amino-terminal propeptide of type III procollagen, PIIINP (MMRM)
    iii. Change in hyaluronic acid, HA (MMRM)
h. Change in AST/ALT Ratio (MMRM)
i. Change in Platelet Count (MMRM)
j. Change in ACTITEST Score (MMRM)
k. Change in GAL-3 (biomarker, MMRM)

5. Perform Chi Square Test without correction on overall data as well as the subset Without Varices for the following:
    a. All Complications (for patients with at least one complication)
    b. Each separate complication
    c. Perform all analyses in a through e above also for combined active groups (GR2 + GR8) vs. placebo