Clinical Study Protocol
A Phase 3, Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of Aramchol in Subjects with Nonalcoholic Steatohepatitis (NASH) with Open-Label Part to Evaluate the Safety, PK and Treatment Response Kinetics of Aramchol
The ARMOR Study

Protocol No: Aramchol-018
EUDRACT No: 2019-002073-56
IND: 79,200
Clinical Phase: 3
Protocol Version 4.0 dated 23 Nov 2020

[redacted]

Sponsor: Galmed Research and Development, Ltd.
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Co-Principal Investigators: [redacted]14

Confidentiality Statement

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GCP Statement

This clinical study will be conducted in accordance with the Sponsor's and/or Contract Research Organization's Standard Operating Procedures (SOPs), current Good Clinical Practice (GCP), the provisions of ICH (International Conference on Harmonization) Guidelines, applicable US Code of Federal Regulations (CFR) and EU Directives.

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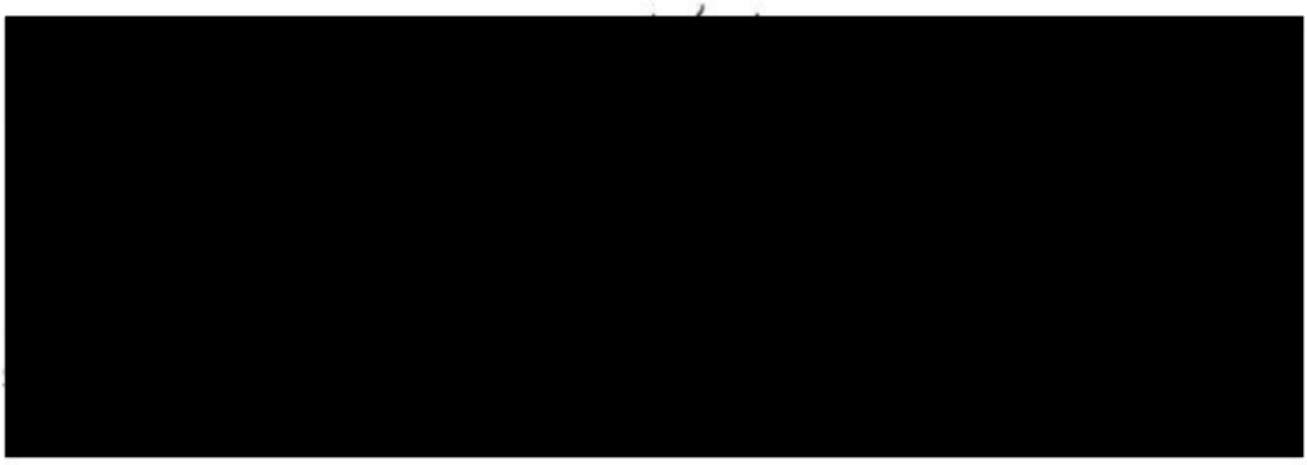


Galmed Research and Development Ltd
ARMOR Study
Protocol No. Aramchol-018

INVESTIGATOR'S AGREEMENT

A Phase 3, Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of Aramchol in Subjects with Nonalcoholic Steatohepatitis (NASH) with Open-Label Part to Evaluate the Safety, PK and Treatment Response Kinetics of Aramchol (The ARMOR Study).

Protocol Version 4.0, dated 23 Nov 2020

I the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws and regulations and standards outlined in the Clinical Trial Agreement.

Principal Investigator's name	Institution name
Institution address	
Principal Investigator's signature	Date

1 SYNOPSIS

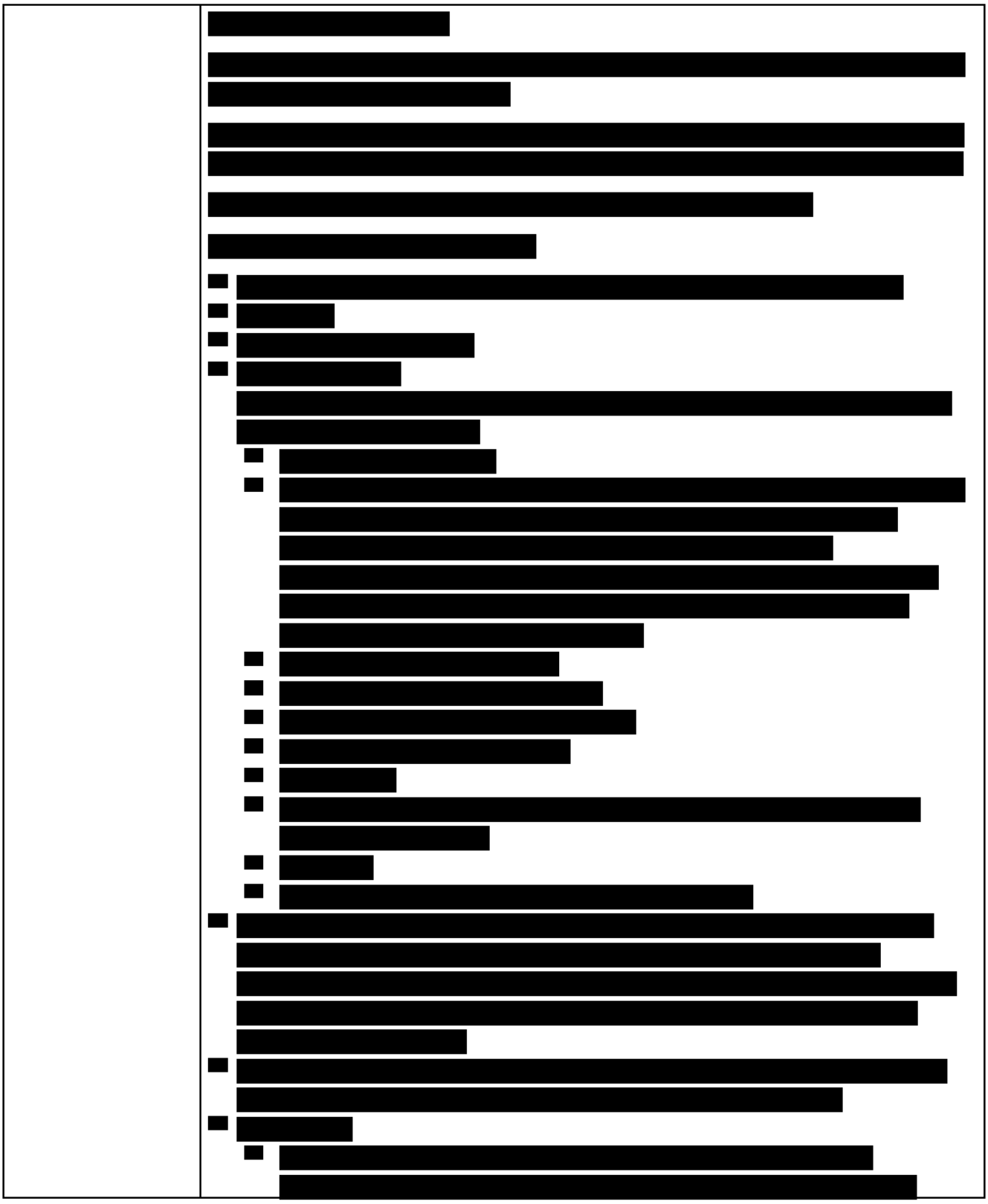
Study Title	A Phase 3, Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of Aramchol in Subjects with Nonalcoholic Steatohepatitis (NASH) with Open-Label Part to Evaluate the Safety, PK and Treatment Response Kinetics of Aramchol (The ARMOR Study)
IND Number	79200
EudraCT	2019-002073-56
Clinical Phase	Phase 3
Investigational Drug	Aramchol
Sponsor Name and Address:	Galmed Research and Development LTD. 16 Ze'ev Tiomkin St. Tel Aviv, 6578317 ISRAEL Tel: 972-3-6938448 Fax: 972-3-6938447
[redacted]	[redacted]
Main Indication	Nonalcoholic Steatohepatitis (NASH)
Study Objectives	**Open-Label Part:** • To evaluate the safety and PK of twice daily administration (BID) of Aramchol 300mg in subjects with NASH and liver fibrosis. • To explore the kinetics of histological outcome measures and Non-Invasive Tests (NITs) associated with NASH and fibrosis for the treatment duration of 24, 48 and 72 weeks. **Randomized, Double-Blind, Placebo-Controlled Part:** To evaluate the efficacy and safety of twice daily administration (BID) of Aramchol 300mg as compared to placebo in subjects with NASH and liver fibrosis.
Study Population	**Open-Label Part**: A total of 150 adult subjects with NASH and fibrosis confirmed by liver histology (F1-F3) **Randomized, Double-Blind, Placebo-Controlled-Part:**

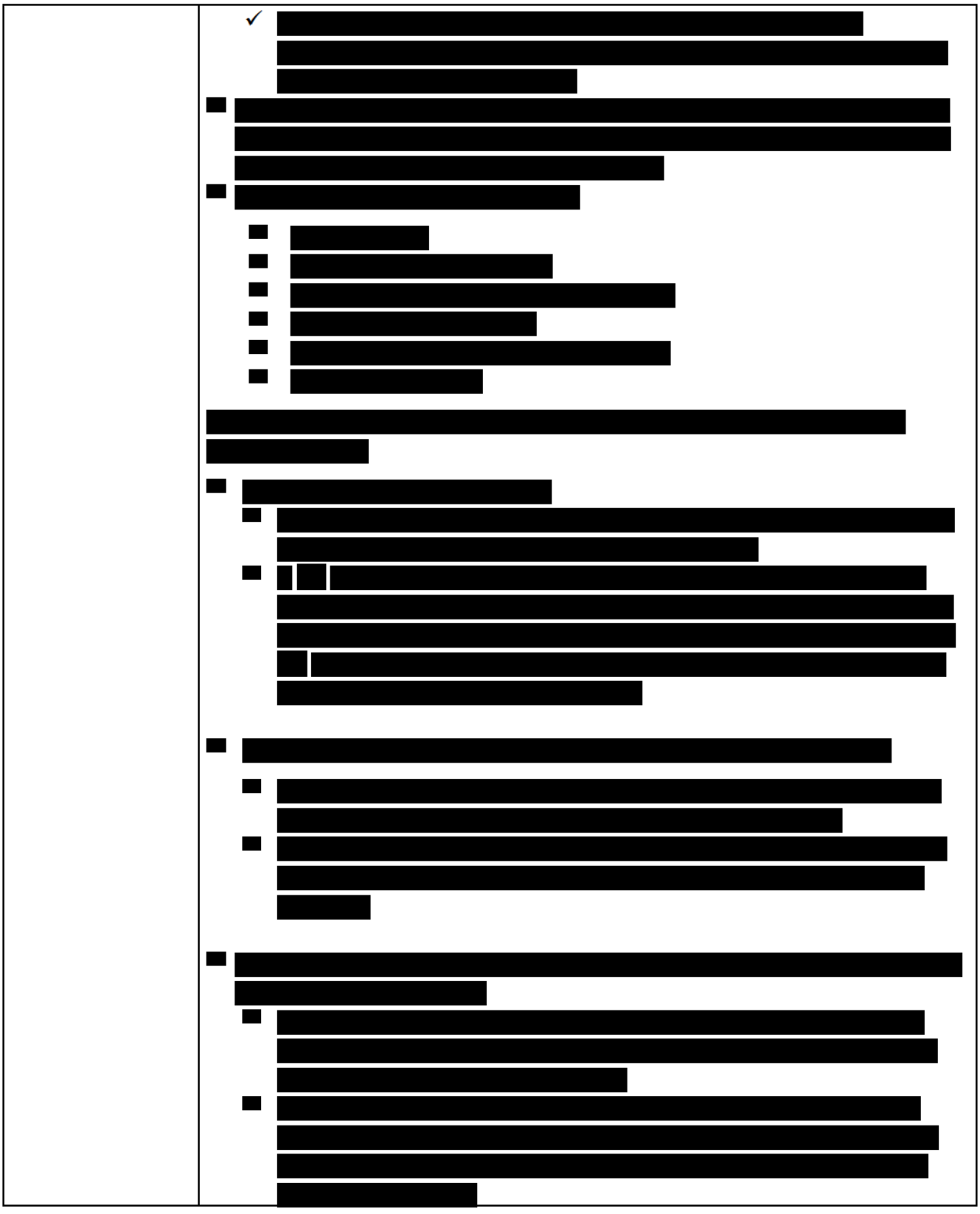
	A total of 2000 adult subjects with NASH and fibrosis confirmed by liver histology (F2-F3) who are overweight or obese and have prediabetes or type 2 diabetes.
Study Groups	**<u>Open-Label Part</u>:** Subjects, including those already randomized to Aramchol 300mg BID or Placebo, will be randomized in a ratio of 1:1:1 to receive Aramchol 300mg BID according to the below grouping: • Group A: The post-baseline liver biopsy will be conducted at week 24 • Group B: The post-baseline liver biopsy will be conducted at week 48 • Group C: The post-baseline liver biopsy will be conducted at week 72 [redacted] **<u>Randomized, Double-Blind, Placebo-Controlled Part</u>:** Subjects will be randomized in a ratio of 2:1 to receive Aramchol 300mg BID or matching placebo, respectively.
Study Design	**<u>Open-Label Part</u>:** A total of 150 subjects including those already randomized to Aramchol 300mg BID or placebo, will be randomized in a ratio of 1:1:1 to receive Aramchol 300mg BID according to the below grouping: • Group A: The post-baseline liver biopsy will be conducted at week 24 • Group B: The post-baseline liver biopsy will be conducted at week 48 • Group C: The post-baseline liver biopsy will be conducted at week 72 In order to more comprehensively explore the kinetics of histological outcome measures (e.g. are there subjects who may not show improvement in histological outcome at week 24, 48 or 72 but may improve with longer duration of treatment), a 2nd post-baseline liver biopsy sample will be collected for subjects whose post-baseline liver biopsy at week 24 or 48 or 72 does not show at least 1 stage improvement in fibrosis (fibrosis non-responders). The 2nd post-baseline liver biopsy sample will be collected 1 year later (i.e. at weeks 72 or 96 or 120 respectively

	The Open-Label Part will continue for the same duration as the Randomized, Double-Blind, Placebo-Controlled Part. All subjects in the Open-Label Part will receive Aramchol 300mg BID until End of study (EoS). Review and assessment of data will be conducted according to a pre-defined schedule (specified in the Statistical Methodology section). **<u>Randomized, Double-Blind, Placebo-Controlled Part</u>:** A total of 2000 subjects will be randomized to receive Aramchol or matching placebo employing a permuted blocks of 2:1 randomization scheme, respectively. The Randomized, Double-Blind, Placebo-Controlled Part consists of 2 phases; an initial phase with a Histology-Based endpoint, and a subsequent Phase with a Clinically-Based endpoint. Throughout the duration of both study phases, subjects will be treated with either Aramchol or matching placebo according to the randomization scheme generated prior to study initiation. [redacted] In order to preserve the integrity of the Randomized, Double-Blind, Placebo-Controlled Part the following will be performed: • Subjects, sites and Sponsor personnel will be kept blinded to treatment assignment until EoS.

	[redacted] Both study Parts (Open-Label Part and Randomized, Double Blind, Placebo-Controlled Part) will be closely monitored by an unblinded independent Data Monitoring Committee (DMC) according to a pre-defined DMC charter. The DMC will meet periodically (at least every 3-4 months) assess the ongoing accumulated study data to ensure study subject welfare. Clinical outcome events, possible DILI and major adverse cardiovascular events (MACE) will be adjudicated by the following independent adjudication committees for both study Parts (Open-Label Part and Randomized, Double Blind, Placebo-Controlled Part): • **Clinical Outcome Adjudication Committee (COAC)** will adjudicate predefined clinical outcome events (all-cause mortality, liver transplant, progression to cirrhosis, change in MELD score to > 15 and hospitalization due to hepatic decompensation events). • **Cardiac Adjudication Committee (CAC)** will adjudicate Major Adverse Cardiovascular Events (cardiovascular death non-fatal myocardial infarction, non-fatal stroke), hospitalization for unstable angina or heart failure, and all-cause mortality. • **Hepatic Safety Adjudication Committee (HSAC)** will adjudicate hepatic safety events including cases of suspected DILI as well as non-endpoint hepatic/hepatobiliary SAEs.

Duration	**<u>Open-Label Part</u>:** • **Screening:** up to 8 weeks **Treatment period:** The Open-Label Part will continue for the same duration as the Randomized, Double-Blind, Placebo-Controlled Part. All subjects in the Open-Label Part will receive Aramchol 300mg BID until End of study (EoS). **<u>Randomized, Double-Blind, Placebo-Controlled Part</u>:** • **Screening:** up to 8 weeks • **Treatment period:** Subjects will remain on the same treatment assignment for up to 7 years. • **End of study:** All 2000 subjects planned to be randomized into this study will receive Aramchol or matching placebo until End-of-Study (EoS) which will occur at the time when a total of 380 subjects will experience at least 1 pre-clinical event or at 5 years from last subject' randomization, whichever comes first. • **Extension study**: Subjects that complete 7 years in the study or that are ongoing at EoS will be provided the option to receive Aramchol treatment in an open-label extension. The extension study will be detailed under a separate protocol.
Number of Sites	**<u>Open-Label Part</u>**: Approximately 40 **<u>Randomized, Double-Blind, Placebo-Controlled Part:</u>** Approximately 200
Number of Subjects	**<u>Open-Label Part</u>:** A total of 150 subjects. **<u>Randomized, Double-Blind, Placebo-Controlled Part</u>:** A total of 2000 subjects.
Study Drug Administration	**<u>Open-Label Part</u>:** Aramchol 300mg BID **<u>Randomized, Double-Blind, Placebo-Controlled Part</u>:** Aramchol 300mg BID or matching placebo.
Study Visits	**Schedule of activities for both study Parts:** With the exception of the timing of the biopsies and analysis of microbiome, all study procedures of the Open-Label Part will be similar to the Randomized, Double-Blind, Placebo-Controlled Part.





	✓ [redacted]

	✓ [redacted]
Background:	Nonalcoholic steatohepatitis (NASH) is a subset of nonalcoholic fatty liver disease (NAFLD), a broad term that encompasses the entire spectrum of fatty liver diseases in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis to cirrhosis. NASH is a histological definition, requiring the presence of ≥5% hepatic steatosis with inflammation and hepatocyte injury (ballooning) with or without fibrosis. NASH promotes liver fibrosis and some patients progress to severe hepatic diseases, including cirrhosis and liver failure. Patients who have NASH may also develop hepatocellular carcinoma, and/or require liver transplantation for end-stage liver disease or hepatocellular carcinoma. NASH is the second leading cause of cirrhosis among adults awaiting liver transplantation in the United States, while NAFLD is the third most common cause of hepatocellular carcinoma in the United States. Liver-related mortality is increased 10-fold in NASH patients compared with the general population. Additionally, NASH patients have an increased rate of cardiovascular events and are at a higher risk of cardiovascular mortality. Aramchol is a novel fatty acid-bile acid conjugate targeted to the liver that induces beneficial modulation of intrahepatic lipid metabolism. In non-clinical studies, the effect of Aramchol on fibrosis was shown to be indirect via

	reduction of steatosis and ballooning, and direct via reduction of collagen production from human hepatic stellate cells (HSC). Aramchol exerts its anti-steatotic and anti-fibrotic effects via down-regulation of Stearoyl-CoA desaturase-1 (SCD1) expression in hepatocytes and HSCs, resulting in up regulation of ATP-binding cassette transporter ABCA1, improvement of fatty acid oxidation with a concomitant reduction in the generation of oxidative stress and reduction in collagen production. Two Phase 2 clinical studies demonstrated preliminary benefit. The Phase 2a study tested two doses of Aramchol, 100mg and 300mg, against placebo in 60 subjects with NAFLD. There was a statistically-significant dose-response in the relative change in liver fat content between the groups. In the Phase 2b study, 247 subjects with biopsy-proven NASH who were overweight or obese and had prediabetes or T2DM, received Aramchol 400mg QD (n=101), Aramchol 600mg QD (n=98) or placebo (n=48) for 52 weeks with paired MRS and biopsy. At baseline a majority of study participants had advanced disease, 60% with stage 2 or 3 fibrosis and 70% with NAFLD activity score (NAS) ≥5. Both doses of Aramchol reduced liver fat vs placebo (as measured by MRS) with a dose-response for a ≥5% absolute reduction (600mg > 400mg > placebo). Aramchol 600mg showed potential efficacy on the 2 critical histological endpoints for a registrational NASH phase 3 study: NASH resolution without worsening of fibrosis and fibrosis improvement without worsening of NASH. Although limited by sample size and duration, fewer patients progressed to cirrhosis in the 600mg arm. Both Aramchol doses significantly reduced alanine aminotransferase (ALT), aspartate aminotransferase (AST) and HbA1c in a dose- related manner. No differences in body weight were apparent. In this one-year study in patients with NASH and comorbidities, both doses of Aramchol showed a favorable safety and tolerability profile. Almost 90% of subjects in the active-treatment arms completed 52 weeks and 13 weeks of follow-up. No death was reported in the study. Serious adverse events (SAEs) were reported in approximately 10% in each treatment group. SAEs were typical for the patient population. No clustering of event types was noted in the active-treatment arms. Following the dose response pattern demonstrated, an effort was made to increase exposure and potentially increase efficacy. A split dose method was used and a Phase 1 pharmacokinetic (PK) and safety study was conducted, comparing once daily dosing of Aramchol 600mg to twice daily dosing of Aramchol 300mg. Study results showed that all subjects had approximately 50% higher drug concentrations with the 300mg BID regimen vs. 600mg QD.

	Since dose splitting to 300mg BID results in increased exposure providing an opportunity to increase efficacy and in light of the good safety profile observed with Aramchol to date, 300mg BID is the selected dose for clinical studies with Aramchol.
Rationale	The current study is composed of two parts: **An Open-Label Part** to evaluate the safety and PK of Aramchol 300 mg BID in subjects with NASH and liver fibrosis and to explore the kinetics of histological outcomes and NITs associated with NASH and liver fibrosis for the treatment duration of 24, 48 and 72 weeks. The study population includes subjects with NASH and liver fibrosis stage 1-3, subjects with NASH who may or may not be overweight and subjects with NASH who may or may not have T2DM or be pre-diabetic. PK and safety data and information on the kinetics of histological outcomes and NITs from this Open-Label Part will be summarized in support of regulatory submissions. However, histological outcomes and clinical events from the Open-Label Part will not be considered for the Histology-Based primary endpoint and the Clinically-Based primary endpoint of the Randomized, Double-Blind, Placebo-controlled part of the study. Clinical events will instead be reported as safety data. **A Randomized, Double-Blind, Placebo-Controlled Part** to evaluate the safety and efficacy of Aramchol 300 mg BID to support regulatory approval. The study population for this part includes subjects with NASH and liver fibrosis stage 2 and 3 who are overweight and are either pre-diabetic or have T2DM. The Randomized, Double-blind, Placebo-Controlled Part of the study is generally consistent with *FDA Guidance for Industry – Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment (December 2018)* and *EMA Reflection paper on regulatory requirements for the development of medicinal products for chronic noninfectious liver diseases (PBC, PSC, NASH) (November 2018),* and is intended to demonstrate the effectiveness and safety of Aramchol to support regulatory approval. [redacted]

	✓ [redacted] ✓ The open label part of the study will provide additional safety and PK information for Aramchol 300 mg BID in subjects with NASH while enrollment in the Randomized, Double-blind, Placebo-controlled Part of the study is pending. Long-term safety data from this study will ultimately be a valuable addition to Aramchol safety database. The kinetics of histological outcomes and NITs for NASH associated with liver fibrosis have not been well characterized for NASH (e.g. how early can a beneficial effect on fibrosis be observed, are there subjects that improve with longer duration of therapy etc.). Phase 2 NATIVE study with lanifibranor, cohort 4 in the Phase 2 study with aldafermin, BALANCED Phase 2a study with efruxifermin) suggest that favorable effects may be observed as early as at week 16; other studies have reported longer times to observed effect including up to 96 weeks in the PIVENS study with pioglitazone. However, no study, yet, has examined within one clinical setting the kinetics of histological outcome measures for the different treatment duration. The Phase 2b ARREST study had a 52-week endpoint for which favorable effects were observed. However, it is not known how early a treatment effect may be observed and

	what the difference may be for histological outcomes and NITs between a treatment duration of 24, 48 or 72 weeks. The Open-Label Part will provide data to help characterize the kinetics of histological outcomes and NITs for Aramchol.
Inclusion Criteria	The inclusion criteria for the Open-Label Part are the same as those of the Randomized, Double-Blind, Placebo-Controlled Part with the exception of fibrosis stage (the Open-Label Part allows enrollment of subjects with fibrosis stage 1), weight (the Open-Label Part allows enrollment of subjects who are not overweight) and Type diabetes mellitus (the Open-Label Part allows enrollment of subjects who are not prediabetic or subjects who do not have type 2 diabetes mellitus). 1. Male or female age 18 to 75 years (inclusive at first Screening visit) 2. Histological confirmation of NASH on a diagnostic liver biopsy by central reading of the slides • Open-Label Part: biopsy obtained within 9 months prior to randomization or during the screening period • Randomized, Double-Blind, Placebo-Controlled Part: biopsy obtained within 6 months prior to randomization or during the screening period 3. Total NAS Score 4 or more with at least 1 in each component of the NAS Score (steatosis ≥1 AND inflammation ≥1 AND ballooning ≥1) 4. Fibrosis Stage must be 2 or 3 • Open-Label Part may include up to 30 subjects with fibrosis stage 1 5. [redacted] 6. Body mass index (BMI) • Open-Label Part: ≤ 40 kg/m2 • Randomized, Double-Blind, Placebo-Controlled Part: between 25kg/m^2 and 40 kg/m^2 7. [redacted]

8. Randomized, Double-Blind, Placebo-Controlled Part only: Type 2 diabetes mellitus or prediabetes: Type 2 diabetes diagnosis must be established and documented prior to screening.

[redacted]

9. For subjects with type 2 diabetes, glycemia must be controlled (HbA1c ≤ 9%)

10. Negative blood pregnancy test at study entry for females of childbearing potential confirmed by central laboratory

11. [redacted]

	[redacted] 12. Able to understand the nature of the study and to provide signature of the written informed consent
Exclusion Criteria	All exclusion criteria for the Open-Label Part are the same as those of the Randomized, Double-Blind, Placebo-Controlled Part. 1. Histologically documented liver cirrhosis (fibrosis stage 4) 2. Inability or unwillingness to undergo a liver biopsy 3. Abnormal synthetic liver function • [redacted] [redacted] [redacted] 4. ALT or AST > 5× upper limit of normal (ULN); according to central laboratory 5. Platelet count < 150,000mm^3 6. Alkaline phosphatase ≥2× ULN 7. Known or suspected hepatocellular carcinoma (HCC) 8. Model for End-Stage Liver Disease (MELD) score > 12 using OPTN formula 9. [redacted] 10. Prior history or presence of decompensated liver disease 11. [redacted] 12. Other (acute or chronic) coexisting liver disease based on medical history and/ or centralized review of liver histology [redacted] • [redacted] [redacted] [redacted] [redacted] [redacted] • [redacted] [redacted] [redacted]

	• [redacted] [redacted] 13. Known alcohol and/or any other drug abuse or dependence in the last five years • [redacted] 14. [redacted] [redacted] 17. Weight loss of more than 5% within 3 months prior to screening 18. History of bariatric surgery within 5 years of liver biopsy or planned surgery for weight reduction 19. Treatment with drugs that may cause NAFLD within 12 months prior to the biopsy [redacted] 20. [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] 25. Current or planned treatment with immunosuppressive drugs (e.g. adalimumab, azathioprine and methotrexate) 26. Evidence of any other unstable or untreated clinically significant hepatic, cardiovascular (including any clinically significant cardiovascular events within 3 months before screening), pulmonary, immunological,

	endocrine, hematological, gastrointestinal, neurological, neoplastic or psychiatric disease • [redacted] 27. History or presence of any disease or condition known to interfere with the absorption, distribution, metabolism or excretion of drugs including bile salt metabolism (e.g. inflammatory bowel disease (IBD); major previous or planned intestinal operation (ileal or involving the right colon); chronic pancreatitis; celiac disease or previous vagotomy) 28. Chronic antibiotic treatment (e.g. rifaximin) 29. Uncontrolled hypertension • [redacted] 30. [redacted] 38. Any other condition that in the opinion of the Investigator warrants exclusion from the study 39. [redacted]
Efficacy Endpoints	**<u>Open-Label Part</u>:** **Primary kinetics Endpoints:** The primary endpoints are the kinetics of the following histological outcome measures for treatment duration of 24, 48 and 72 weeks and potentially following a 2nd post-baseline biopsy at weeks 72 or 96 or 120, respectively: • **Improvement in Fibrosis** defined as the Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to one stage (NASH

	CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation or steatosis) • **Resolution of NASH** defined as the Proportion (%) of subjects with resolution of NASH (defined by ballooning of 0 and inflammation 0-1) and no worsening of liver fibrosis on NASH CRN fibrosis score (≥ 1 stage increase). **Secondary kinetics Endpoints:** The secondary endpoints are the kinetics of the following parameters and NITs for the treatment duration of 24, 48 and 72 weeks: • ALT and AST • Glycemic parameters • Lipid parameters • Fibroscan • Biomarkers including but not limited to ProC3 and ELF • Microbiome profile **<u>Randomized, Double-Blind, Placebo-Controlled Part</u>:** **Primary Efficacy Endpoints**: The Randomized, Double-Blind, Placebo-Controlled Part will utilize 2 primary efficacy endpoints; Histology-Based primary endpoint and Clinically-Based primary endpoint. Meeting the Histology-Based primary endpoint will serve as the basis for the submission of a marketing authorization application under regulatory provisions of accelerated/conditional approval. Meeting the Clinically-Based endpoint will provide confirmation of clinical benefit. The primary efficacy endpoints for the Randomized, Double-Blind, Placebo-Controlled Part are: • <u>Histology-Based</u>: The Histology-Based primary endpoint will be derived from the week 72 biopsy of the initial 1000 subjects as compared to baseline biopsy and will use: ✓ **Resolution of NASH** defined as the Proportion (%) of subjects with resolution of NASH (defined by Ballooning of 0 and inflammation 0-1) and no worsening of liver fibrosis on NASH CRN fibrosis score (≥ 1 stage increase). OR ✓ **Improvement in Fibrosis** defined as the Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis

	(defined as no increase in NAS for ballooning, inflammation or steatosis) • Clinically-Based: The Clinically-Based primary endpoint is the time to first occurrence of any of the following adjudicated events: ✓ All-cause mortality ✓ Liver transplant ✓ Histological progression to cirrhosis ✓ MELD score >15 if baseline MELD score was <12 ✓ Hospitalization due to hepatic decompensation event(s) including: - Hepatic encephalopathy grade ≥2 (as assessed by West Haven scale) - Variceal bleeding - New onset ascites requiring treatment - Spontaneous bacterial peritonitis as assessed by either positive cell culture or cell count Events will be adjudicated by the independent Clinical Outcome Adjudication Committee (COAC). **Key Secondary Efficacy Endpoint:** • At EoS, **Improvement in Fibrosis:** 5-Year Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation or steatosis) **Exploratory Endpoints:** • At the time of the Histology-Based analysis: ✓ **Pathologist NASH resolution assessment:** Week 72 Proportion (%) of subjects with NASH resolution as defined by the pathologist overall assessment of change from presence of definite steatohepatitis at baseline to absence of definite steatohepatitis (without worsening of fibrosis) ✓ **Two-Stage Improvement in Fibrosis**: Week 72 Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to two stages and no worsening of NASH (defined as no increase in NAS for ballooning, inflammation, or steatosis). ✓ **NASH Resolution AND Improvement in Fibrosis**: Week 72 Proportion (%) of subjects with both Resolution of NASH and Improvement in Fibrosis. ✓ **Fibrosis Resolution:** Week 72 Proportion (%) of subjects with resolution of fibrosis (defined as fibrosis stage 0).

	✓ **Fibrosis Improvement:** Week 72 Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) ✓ **Fibrosis Worsening:** Week 72 Proportion (%) of subjects with worsening in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) ✓ Ballooning 0: Week 72 Proportion (%) of subjects with ballooning of 0 ✓ Change from baseline to week 72 in ALT. ✓ Change from baseline to week 72 in Glycemic parameters (including HbA1c, fasting glucose, fasting insulin, C-peptide, and HOMA- IR). ✓ Change from baseline to week 72 in AST Change from baseline to week 72 in lipid parameters (including total cholesterol, LDL-C, apoB, non- HDL cholesterol, HDL cholesterol, and triglycerides)
Safety Evaluation	**Safety and Tolerability Evaluations** 1. Adverse events and serious adverse events. 2. Safety laboratory evaluations. 3. Vitals signs. 4. 12-Lead ECG. 5. Physical examinations. 6. Drop-out rates.
Pharmacokinetics Endpoints	Plasma concentrations of Aramchol will be subjected to population pharmacokinetic analysis using NONMEM software. In addition to variability in the whole population that have received treatment with Aramchol, the relationships between the population PK profiles and factors such as demography, duration of treatment, concomitant medications, severity of disease and response to treatment will be examined.
Statistical Methodology	This study, which consists of two parts, is designed as follows: • Open-Label Part: To explore the kinetics of histological outcome measures and Non-Invasive Tests (NITs) associated with NASH and fibrosis for the treatment duration of 24, 48 and 72 weeks. • Randomized, Double-Blind, Placebo-Controlled Part: To evaluate the efficacy and safety of twice daily administration (BID) of Aramchol 300mg as compared to placebo in subjects with NASH and liver fibrosis. **Open-Label Part**: A total of 150 subjects, including those already randomized to Aramchol 300mg BID or placebo, will be randomized in a ratio of 1:1:1 to receive Aramchol 300mg BID according to the below grouping: • Group A: The post-baseline liver biopsy will be conducted at week 24 • Group B: The post-baseline liver biopsy will be conducted at week 48

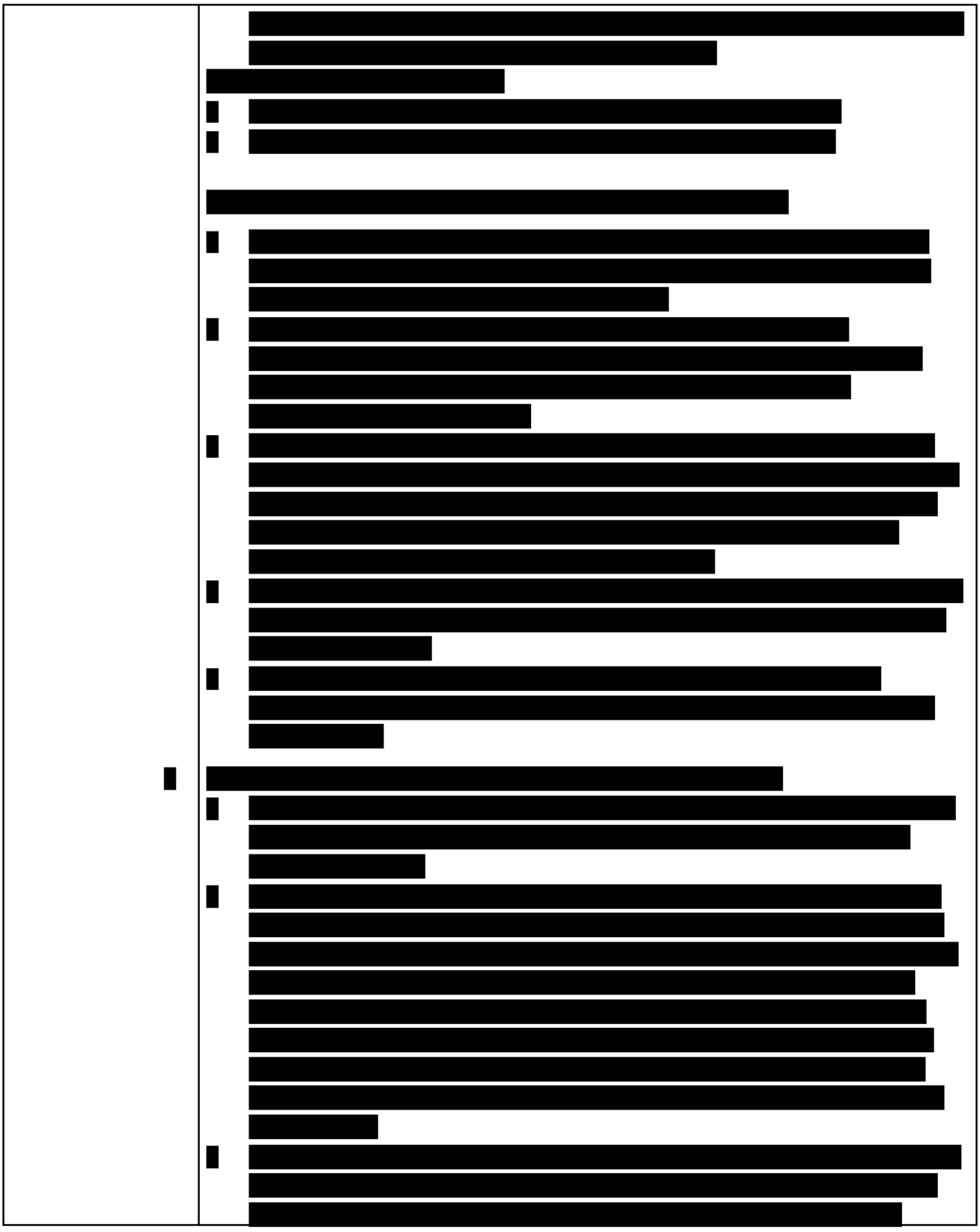
	• Group C: The post-baseline liver biopsy will be conducted at week 72 Randomization in the Open-Label Part will employ a semi-minimization algorithm to balance the 3 groups in number of subjects, distribution of subjects according to fibrosis score (F1, F2 and F3), presence or absence of T2DM, and prior exposure to Aramchol 300mg BID. F1 subjects will be capped to enroll no more than 30 subjects. In order to more comprehensively explore the kinetics of histological outcome measures across treatment duration, a 2nd post-baseline liver biopsy sample will be collected for subjects whose post baseline liver biopsy at week 24 or 48 or 72 does not show at least 1 stage improvement in fibrosis (fibrosis non-responders). The 2nd post-baseline liver biopsy sample will be collected 1 year later (i.e. at weeks 72 or 96 or 120 respectively). The Open-Label Part will continue for the same duration than the Randomized, Double-Blind, Placebo-Controlled Part. All subjects in the Open-Label Part will receive Aramchol 300mg BID until End of study (EoS). Review and assessment of data will be conducted according to a pre-defined schedule: • The 1st data assessment which will be limited to NITs analyses will occur at a time when approximately one third of the study population has completed 24 weeks of treatment. • The 2nd data assessment will occur at a time when approximately one third of the study population has undergone the post-baseline liver biopsy. Assessments will include analysis of histological endpoints and NITs. • The 3rd data assessment will occur at a time when approximately two-thirds of the study population have undergone the post-baseline liver biopsy. Assessments will include analysis of histological endpoints and NITs. • The 4th data assessment for assessing the kinetics of the histological outcome measures and NITs for the duration of 24, 48 and 72 weeks will be conducted at the time when all randomized subjects have undergone the post-baseline liver biopsy. • A potentially 5th data assessment for further assessing the kinetics of the histological outcome measures and NITs for treatment duration of 24, 48 and 72 weeks and potentially following a 2nd post-baseline biopsy at weeks 72 or 96 or 120, respectively, will be conducted at the time when the last randomized subjects have underwent the last post-baseline liver biopsy. The planned sample size of a total of 150 subjects is considered appropriate for assessing the kinetics of histological outcome measures and NITs associated with NASH and fibrosis for the treatment duration of 24, 48 and 72 weeks. The overall alpha level for the Open-Label Part is 0.05 using 2-tailed tests. No multiplicity adjustment is planned as this study part is exploratory in nature.

Statistical analysis of efficacy endpoints will use the modified intent to treat (mITT) Analysis Set employing various regression models designed to explore the kinetics of histological outcome measures and NITs as a function of treatment duration.

A more detailed Statistical Analysis Plan (SAP) dedicated for the Open-Label Part will be developed prior to the conduct of the 1st data evaluation.

	• [redacted] **Primary Study Efficacy Endpoints:** The primary efficacy endpoints for this study are: • Histology-Based: **Resolution of NASH** OR **Improvement in Fibrosis** • Clinically-Based: Time to first occurrence of the adjudicated events **Schedule of Statistical Analyses:** Statistical analyses of efficacy endpoints are planned to be performed at two study milestones: • The Histology-Based primary endpoint will be analyzed at the time when the initially randomized 1000 subjects have performed the week 72 visit or terminated early. • The Clinically-Based primary endpoint will be analyzed at EoS, when all 2000 subjects planned to be randomized into this study will receive Aramchol or matching placebo until EoS which will occur at the time when a total of 380 subjects will experience at least 1 pre-specified clinical event or at 5 years from last subject randomization, whichever comes first. **Principal Analysis Set for Efficacy Inference:** The principal analysis set for efficacy inference will be the Intention-to-Treat (ITT) Analysis Set which will include all randomized subjects as follows: • The Histology-Based primary endpoint will employ the Histology-Based-ITT Analysis Set including all initially 1000 randomized subjects. • The Clinically-Based primary endpoint will employ the Clinically-Based-ITT Analysis Set including all randomized subjects. **Type-I Error and Multiplicity Adjustment:** The overall alpha level for this study is 0.05 using 2-tailed tests. All significance testing for this study will use two-tailed tests. The Histology-Based primary endpoint will use an alpha level of 0.02 and adjustment for multiplicity for the two alternatives proposed (Resolution of NASH, or, Improvement in Fibrosis) will use the Truncated Hochberg's procedure with gamma=0.1. The Clinically-Based primary endpoint will use an alpha level of 0.03, or 0.05 in case that both alternatives proposed for Histology-Based primary endpoint were met (no key secondary endpoints are defined for the Histology-Based study part). The sole key secondary endpoint for the Clinically-Based study part will use the alpha level used for the Clinically-Based primary endpoint in case that the later "wins".

[redacted]



	[redacted]

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	American diabetes association
AE	Adverse events
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
ATP	Adenosine triphosphate
AUC	area under the <plasma> drug concentration by time curve
AUC_{0-t}	area under the <plasma> drug concentration by time curve for 1 dosing interval of a multiple-dose regimen
BMI	body mass index
BUN	blood urea nitrogen
CDMS	clinical data management system
CFR	Code of Federal Regulations
CGR	Country geographic region
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed plasma drug concentration
CPK	creatine phosphokinase
CRF	case report form (refers to any media used to collect study data [i.e., paper or electronic])
CRO	contract research organization
CS	Compound Symmetry
CSC	Clinical Supply Chain
CSH	Heterogenous Compound Symmetry
CTFG	Clinical Trial Facilitation Group
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiography, electrocardiogram
EMA	European Medicines Agency
EoS	End-of-Study
ESD	Early Study Discontinuation
ET	Early termination
ETD	Early Treatment Discontinuation
EU	European Union
FABAC	Fatty acid-bile acid conjugates
FAS	full Analysis Set
FCS	Fully Conditional Specification
FDA	US Food and Drug Administration
FMD	Flow mediated dilation
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transpeptidase

Abbreviation	Term
GI	gastrointestinal
GMP	Good manufacturing practice
H&E	Hematoxylin & Eosin
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HDL	High density lipoprotein
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HSC	Hepatic stellate cells
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medical product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	intent-to-treat
LDH	lactate dehydrogenase
LSM	liver stiffness measurement
MACE	Major adverse cardiovascular events
MAD	Multiple ascending dose
MAR	Missing at random
max	maximum
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model of end-stage liver disease
MetS	Metabolic syndrome
MI	Multiple Imputations
ML	Maximum-Likelihood
MRS	Magnetic resonance spectroscopy
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Nonalcoholic steatohepatitis
NDA	New drug application
NITs	Non-Invasive Tests
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drugs
OPTN	Organ Procurement and Transplantation Network
OTC	over-the-counter
PBC	Primary biliary cholangitis
PBPK	Physiologically based pharmacokinetic

Abbreviation	Term
PCS	Potential Clinical Significance
PGx	pharmacogenetic(s)
PI	Principal Investigator
PK	pharmacokinetics
PNPLA3	Patatin-like phospholipase domain-containing protein 3
PP	Per-protocol
PSC	Primary sclerosing cholangitis
PT	Preferred Term
QA	quality assurance
QC	quality control
RBC	red blood cell
REML	Restricted Maximum-Likelihood
RTSM	Randomization & Trial Supply Management
SAE	Serious adverse effects
SAP	Statistical Analysis Plan
SCD1	Stearoyl Coenzyme A Desaturase 1
SD	standard deviation
SDV	source document verification
SE	standard error
SOC	system organ class
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
T2DM	Type-2 diabetes mellitus
TEAE	Treatment Emergent Adverse Events
t_{max}	time to maximum observed drug concentration
TSH	thyroid stimulating hormone
ULN	upper limit of the normal range
US(A)	United States (of America)
UTI	Urinary tract infection
WBC	white blood cell
WHO	World Health Organization
WHO Drug	World Health Organization (WHO) drug dictionary

3 INTRODUCTION

3.1 Background Information

3.1.1 Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

Nonalcoholic steatohepatitis (NASH) is the progressive form of nonalcoholic fatty liver disease (NAFLD), a broad term that encompasses the spectrum of fatty liver diseases ranging from simple steatosis to steatohepatitis, fibrosis and cirrhosis in individuals without significant alcohol consumption or secondary causes of steatosis. NASH is a histological definition, requiring the presence of ≥5% hepatic steatosis with inflammation and hepatocyte injury (ballooning) with or without fibrosis[1].

NAFLD is the most prevalent form of chronic liver disease in the world, paralleling the epidemic of obesity and obesity-related complications such as type 2 diabetes mellitus and metabolic syndrome[1,2]. A recent meta-analysis estimated that approximately 25% of the world's population has NAFLD[2] with a projected increase of 30% between 2016 and 2030[3]. The prevalence of NASH is challenging to assess because of the biopsy-based definition. Based on the prevalence of NASH among NAFLD patients who had liver biopsies, the prevalence of NASH in the general population is estimated at 1.5% -6.45%[2], with a projected increase in prevalence of 15%-56% between 2016 and 2030[3]. Features of metabolic syndrome are not only highly prevalent in patients with NAFLD, but also increase the risk of developing NAFLD. Patients with type 2 diabetes have a high prevalence of NAFLD, NASH and advanced stages of fibrosis[1].

The natural history of NAFLD is associated with liver histology at the time of presentation. Patients with simple steatosis are likely to have a benign course, while about 30-50% of patients with NASH develop progressive fibrosis, increasing their risk for cirrhosis and its complications[4,5]. Both disease activity (quantified by NAFLD activity score (NAS)) and fibrosis stage affect the risk for progression to cirrhosis. Fibrosis is staged from 0-4 in relation to the extent of the scarring as follows: Stage 1, zone 3 perisinusoidal fibrosis; Stage 2, as above with portal fibrosis; Stage 3, as above with bridging fibrosis; and Stage 4, cirrhosis (NASH/CRN Brunt/Kleiner scale)[6]. The NASH CRN fibrosis staging system has been validated with respect to the intraobserver and interobserver concordance and sensitivity to change[7]. The progression from NASH without fibrosis through various stages of fibrosis is not linear; however, NASH with fibrosis stages 2 and 3 has a significantly higher risk of progression to cirrhosis within a 10-year time frame and an increased mortality risk compared to lower stages (0-1) of disease[8]. In fact, the presence of significant fibrosis is the best predictor of liver-related and all-cause mortality in NASH[9–11].

NASH is recognized as a major cause of chronic liver disease leading to cirrhosis, liver transplantation and hepatocellular carcinoma (HCC): NASH is the second leading etiology of cirrhosis among adults awaiting liver transplantation in the United States, while NAFLD is the third most common cause of HCC in the United States[1]. Liver-related mortality is increased 10-fold in NASH patients compared with the general population. Additionally, NASH patients have an increased rate of cardiovascular events and neoplasia and are at a higher risk for

cardiovascular-related mortality[1]. With the increasing prevalence of metabolic syndrome and subsequently, NAFLD, NASH, cirrhosis and complications, substantial clinical and economic burdens are inevitable[12].

There are currently no approved medications for NASH and management focuses on lifestyle modifications including diet and exercise. A 2018 guidance from the American Association for the Study of Liver Diseases aims for a reduction in body weight of 3%-5% to achieve improvement in steatosis and 7%-10% to improve the majority of histopathological features of NASH, including fibrosis. The guidance also recognizes the use of a number of medications available for other uses and treatment modalities such as Vitamin E, Pioglitazone and bariatric surgery for the improvement of liver disease in patients with biopsy-proven NASH and fibrosis.

3.2 Aramchol

Aramchol is a novel synthetic small molecule, a conjugate of two components; cholic acid (bile acid) and arachidic acid (saturated fatty acid), linked by a stable amide group. Aramchol is the first in a new pharmacological class of fatty acid-bile acid conjugates (FABACs).

Aramchol affects Stearoyl Coenzyme A Desaturase 1 (SCD1), a key liver enzyme involved in regulating lipid metabolism. In animal models of NASH, it has been demonstrated that Aramchol down-regulates steatosis, ballooning, inflammation and fibrosis. The effect of Aramchol on fibrosis is indirect via reduction of steatosis and ballooning, and direct via reduction of collagen production from human hepatic stellate cells (HSCs).

Phase 1 studies showed a less than dose-proportional increase in the mean Aramchol exposure (1.6-fold between 200mg and 400mg and a 1.2-fold between 400mg and 600mg multiple doses), and a 2.6-fold exposure after a high-fat high-calorie meal as compared to a fast state. Dividing Aramchol to two 300mg doses Q12h resulted in an average increase of approximately 50% in the 24-hour plasma concentrations relative to the levels found with a single daily dose of 600mg Q24h.

In the Phase 2a study, a statistically-significant reduction in liver fat compared to placebo was seen after 3 months of treatment. All AEs in the treated arms were mild or moderate and none were serious. None of the patients withdrew as a result of AEs.

In the Phase 2b ARREST study, 247 subjects with biopsy-proven NASH who were overweight or obese and had prediabetes or type 2 diabetes mellitus were randomized (2:2:1) to receive once daily Aramchol 400mg (n=101), Aramchol 600mg (n=98) or placebo (n=48). Baseline histology of enrolled patients demonstrated a population with advanced disease, with 60% having stage 2 and 3 fibrosis and 70% having NAS ≥5. Subjects underwent both MRS and a biopsy at Baseline and at Week 52 (termination), which were centrally-read by an assessor blinded to treatment allocation.

Almost 90% of subjects in the active-treatment arms completed 65 weeks (52 weeks of treatment and 13 weeks of follow-up) in the study. The incidence of early termination (ET) due to AEs was very low and similar across study arms.

Results showed a statistically-significant reduction in liver fat with Aramchol 400mg (p=0.0450) but not with 600mg (p=0.0655) compared to the placebo arm, despite similarity in the magnitude of treatment effect in the 400mg and 600mg arms. A post-hoc analysis showed statistically-significant ≥5% absolute reduction in liver fat in 47% of patients treated with Aramchol 600mg vs. 24% with placebo (p<0.028) and 37% with 400mg, suggesting a dose-response pattern.

Biopsy results, key for further assessment in a NASH pivotal study, showed that significantly more patients treated with Aramchol 600mg vs. placebo achieved NASH resolution without worsening of fibrosis (16.7% vs. 5.0%; p=0.0514); and that a larger proportion of patients showed at least a one point improvement in fibrosis stage without worsening of NASH in Aramchol 600mg vs. placebo (29.5% vs. 17.5%; p=0.2110). Only 1 patient (1.3%) progressed to cirrhosis in the Aramchol 600mg arm whereas 6 (7.5%) and 3 (7.5%) patients reached this endpoint in the 400mg and placebo arms, respectively.

Both doses significantly reduced alanine aminotransferase (ALT) (p<0.001), aspartate aminotransferase (AST) (p=0.002) and HbA1c (p<0.007) vs. placebo in a dose-dependent manner.

Aramchol continued to show a favorable safety and tolerability profile. No death was reported in the study. SAEs were reported in approximately 10% of subjects. Each SAE was reported for a single subject, SAEs were typical for the patient population and no clustering of event types was noted in the active-treatment arms. Most AEs in the study were mild and recovered.

For a detailed description of the clinical and non-clinical development program of Aramchol refer to the current IB.

3.3 Known and Potential Risks and Benefits to Human Subjects

Aramchol is a novel fatty acid-bile acid conjugate targeted to the liver that induces beneficial modulation of intrahepatic lipid metabolism. In non-clinical studies, the effect of Aramchol on fibrosis was shown to be indirect via reduction of steatosis and ballooning, and direct via reduction of collagen production from human HSC.

In the Phase 2b ARREST study, Aramchol 600mg once daily showed potential efficacy on the two biopsy endpoints that may currently constitute a primary endpoint for a Phase 3 study; NASH resolution and no fibrosis worsening as well as Improvement in Fibrosis and no NASH worsening.

In this one-year study, in patients with NASH and comorbidities, both doses of Aramchol showed a favorable safety and tolerability profile. No death was reported in the study. SAEs were reported in approximately 10% of subjects. Each SAE was reported for a single subject, and SAEs were typical for the patient population. No clustering of event types was noted in the active-treatment arms. The leading causes for ET were consent withdrawal and AEs. The incidence of ET due to AEs was very low and similar across study arms.

Most AEs in the study were mild and recovered. The proportion of severe events was overall low in all treatment arms and no differences were noted in incidence of severe AEs between arms.

[redacted] of Aramchol for NASH in this Phase 3 clinical study.

The study design employs risk-mitigation measures, with extensive safety monitoring that includes recording and monitoring of adverse events, safety laboratories, vital signs and physical examinations as well as stopping rules and special warnings and precautions for use. The study will be followed by a DMC that will assess the ongoing safety during the study as well as independent adjudication committees for clinical out-come events, possible DILI events and major adverse cardiovascular events (MACE).

3.4 Rationale for Study Design, Dose and Population

3.4.1 Study Rationale

The current study is composed of two parts:

An Open-Label Part to evaluate the safety and PK of Aramchol 300 mg BID in subjects with NASH and liver fibrosis and to explore the kinetics of histological outcomes and NITs associated with NASH and liver fibrosis for the treatment duration of 24, 48 and 72 weeks. The study population includes subjects with NASH and liver fibrosis stage 1-3, subjects with NASH who may or may not be overweight and subjects with NASH who may or may not have T2DM or be pre-diabetic. PK and safety data and information on the kinetics of histological outcomes and NITs from this Open-label Part will be summarized in support of regulatory submissions. However, histological outcomes and clinical events from the Open-Label Part will not be considered for the Histology-Based primary endpoint and the Clinically-Based primary

endpoint of the Randomized, Double-Blind, Placebo-controlled part of the study. Clinical events will instead be reported as safety data.

A Randomized, Double-Blind, Placebo-Controlled Part to evaluate the safety and efficacy of Aramchol 300 mg BID to support regulatory approval. The study population for this part includes subjects with NASH and liver fibrosis stage 2 and 3 who are overweight and are either pre-diabetic or have T2DM. The Randomized, Double-blind, Placebo-Controlled Part of the study is generally consistent with *FDA Guidance for Industry – Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment (December 2018)* [13] and *EMA Reflection paper on regulatory requirements for the development of medicinal products for chronic noninfectious liver diseases (PBC, PSC, NASH) (November 2018)*[14], and is intended to demonstrate the effectiveness and safety of Aramchol to support regulatory approval. Consistent with regulatory guidance there are two primary endpoints for this part of the study:

- ✓ A Histology-Based primary endpoint that will be analyzed after 1000 subjects have completed 72 weeks. The Histology-Based endpoint data will serve as the basis for the submission of a marketing authorization application under regulatory provisions of accelerated/conditional approval based on a surrogate endpoint.
- ✓ The Clinically-Based primary endpoint that will be analyzed at EoS and will provide confirmation of clinical benefit based on a clinical outcomes endpoint.

[redacted]

- ✓ The open label part of the study will provide additional safety and PK information for Aramchol 300 mg BID in subjects with NASH while enrollment in the Randomized, Double-

blind, Placebo-controlled Part of the study is pending. Long-term safety data from this study will ultimately be a valuable addition to Aramchol safety database.

The kinetics of histological outcomes and NITs for NASH associated with liver fibrosis have not been well characterized for NASH (e.g. how early can a beneficial effect on fibrosis be observed, are there subjects that improve with longer duration of therapy etc.). Phase 2 NATIVE study with lanifibranor[16], cohort 4 in the Phase 2 study with aldafermin[17], BALANCED Phase 2a study with efruxifermin[18]) suggest that favorable effects may be observed as early as at week 16; other studies have reported longer times to observed effect including up to 96 weeks in the PIVENS study with pioglitazone[19]. However, no study, yet, has examined within one clinical setting the kinetics of histological outcome measures for the different treatment duration. The Phase 2b ARREST study had a 52-week endpoint for which favorable effects were observed. However, it is not known how early a treatment effect may be observed and what the difference may be for histological outcomes and NITs between a treatment duration of 24, 48 or 72 weeks. The Open-Label Part will provide data to help characterize the kinetics of histological outcomes and NITs for Aramchol.

3.4.2 [redacted]

[redacted]

3.4.3 Study Population Rationale

Patients with stage 2-3 fibrosis, who are overweight/obese with prediabetes or type 2 diabetes are considered at greatest risk for the negative outcomes of NASH. Features of metabolic syndrome (MetS) are not only highly prevalent in patients with NAFLD, but components of MetS also increase the risk of developing NAFLD. This bidirectional association between NAFLD and components of MetS has been well established. In addition, the presence of an increasing number of metabolic diseases, such as insulin resistance, type 2 diabetes, hypertension, dyslipidemia, and visceral obesity, seems to increase the risk of progressive liver disease. Therefore, patients with NAFLD and multiple risk factors such as type 2 diabetes and hypertension are at the highest risk for adverse outcomes[1]

The Randomized, Double-Blind, Placebo-Controlled Part will enroll adult subjects, 18–75 years old, with NASH and fibrosis (F2-F3) confirmed by liver histology who are overweight or obese and have prediabetes or type 2 diabetes.

The Open-label Part intends to assess the safety, PK and treatment response kinetics of Aramchol 300mg BID in a broader population, including subjects with fibrosis stage 1, subjects who are not overweight, and subjects who do not have T2DM.

In both study parts, patients with cirrhosis, abnormal synthetic liver function and history or presence of decompensated liver disease will not be enrolled to the study.

4 STUDY OBJECTIVES

Open-Label Part:

- To evaluate the safety and PK of twice daily administration (BID) of Aramchol 300mg in subjects with NASH and liver fibrosis.
- To explore the kinetics of histological outcome measures and Non-Invasive Tests (NITs) associated with NASH and fibrosis for the treatment duration of 24, 48 and 72 weeks.

Randomized, Double-Blind, Placebo-Controlled Part:

To evaluate the efficacy and safety of twice daily administration (BID) of Aramchol 300mg as compared to placebo in subjects with NASH and liver fibrosis.

4.1 Efficacy Endpoints

4.1.1 Open-Label Part

Primary kinetics Endpoints:

The primary endpoints are the kinetics of the following histological outcome measures for treatment duration of 24, 48 and 72 weeks and potentially following a 2nd post-baseline biopsy at weeks 72 or 96 or 120, respectively:

- **Improvement in Fibrosis** defined as the Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation or steatosis)
- **Resolution of NASH** defined as the Proportion (%) of subjects with resolution of NASH (defined by ballooning of 0 and inflammation 0-1) and no worsening of liver fibrosis on NASH CRN fibrosis score (≥ 1 stage increase).

Secondary kinetics Endpoints:

The secondary endpoints are the kinetics of the following parameters and NITs for the treatment duration of 24, 48 and 72 weeks:

- ALT and AST
- Glycemic parameters
- Lipid parameters
- Fibroscan
- Biomarkers including but not limited to ProC3 and ELF
- Microbiome profile

4.1.2 Randomized, Double-Blind, Placebo-Controlled Part

Primary Efficacy Endpoints

The primary efficacy endpoints of the Randomized, Double-Blind, Placebo-Controlled Part are:

1. Histology-Based: The Histology-Based primary endpoint will be derived from the week 72 biopsy of the initial 1000 subjects as compared to baseline biopsy and will use:
   - ✓ **Resolution of NASH** defined as the Proportion (%) of subjects with resolution of NASH (defined by Ballooning of 0 and inflammation 0-1) and no worsening of liver fibrosis on NASH CRN fibrosis score (≥ 1 stage increase).

   OR
   - ✓ **Improvement in Fibrosis** defined as the Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation or steatosis)

2. Clinically-Based: The Clinically-Based primary endpoint is time to first occurrence of any of the following adjudicated events
   - ✓ All-cause mortality
   - ✓ Liver transplant
   - ✓ Histological progression to cirrhosis
   - ✓ MELD score >15 if baseline MELD score was <12

- ✓ Hospitalization due to hepatic decompensation event(s) including:
  - Hepatic encephalopathy grade ≥2 (as assessed by West Haven scale)
  - Variceal bleeding
  - New onset ascites requiring treatment
  - Spontaneous bacterial peritonitis as assessed by either positive cell culture or cell count

Events will be adjudicated by the independent Clinical Outcome Adjudication Committee (COAC).

Key Secondary Efficacy Endpoints

The key secondary efficacy endpoint for the Randomized, Double-Blind, Placebo-Controlled Part is:

At EoS, **Improvement in Fibrosis:** 5-Year Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation or steatosis).

Exploratory Endpoints

[redacted]

4.2 Safety and Tolerability Evaluations

1. Adverse events and serious adverse events.
2. Safety laboratory evaluations.
3. Vitals signs.
4. 12-Lead ECG.
5. Physical examinations.
6. Drop-out rates.

4.3 Pharmacokinetic Endpoints

Plasma concentrations of Aramchol will be subjected to population pharmacokinetic analysis using NONMEM software. In addition to variability in the whole population that have received treatment with Aramchol, the relationships between the population PK profiles and factors such as demography, duration of treatment, concomitant medications, severity of disease and response to treatment will be examined.

5 STUDY DESIGN

5.1 Overview and Plan

The current study includes two parts:

Open-Label Part:

A total of 150 subjects including those already randomized to Aramchol 300mg BID or placebo, will be randomized in a ratio of 1:1:1 to receive Aramchol 300mg BID according to the below grouping:

- Group A: The post-baseline liver biopsy will be conducted at week 24
- Group B: The post-baseline liver biopsy will be conducted at week 48
- Group C: The post-baseline liver biopsy will be conducted at week 72

In order to more comprehensively explore the kinetics of histological outcome measures (e.g. are there subjects who may not show improvement in outcome at week 24, 48 or 72 but may improve with longer duration of treatment), a 2nd post-baseline liver biopsy sample will be collected for subjects whose post-baseline liver biopsy at week 24 or 48 or 72 does not show at least 1 stage improvement in fibrosis (fibrosis non-responders). The 2nd post-baseline liver biopsy sample will be collected 1 year later (i.e. at weeks 72 or 96 or 120 respectively

Subjects already randomized and ongoing in the Randomized, Double-Blind, Placebo-Controlled Part in the selected sites participating in the Open-Label part will be given the option to switch to the Open-Label Part.

The Open-Label Part will continue for the same duration than the Randomized, Double-Blind, Placebo-Controlled Part. All subjects in the Open-Label Part will receive Aramchol 300mg BID until EoS.

The study schema of the Open-Label Part is presented in Figure 1

Figure 1: Open-Label Part Schema

Randomized, Double-Blind, Placebo-Controlled Part:

A total of 2000 subjects will be randomized to receive Aramchol or matching placebo employing a 2:1 randomization scheme, respectively.

The Randomized, Double-Blind, Placebo-Controlled Part consists of 2 phases; an initial phase with a Histology-Based endpoint, and a subsequent phase with a Clinically-Based endpoint. Throughout the duration of both study phases, subjects will be treated with either Aramchol or matching placebo according to randomization scheme generated prior to study initiation. The study phases are:

- **Histology-Based phase**:
  The statistical analysis of the Histology-Based primary endpoint will be conducted when the initially randomized 1000 subjects have completed the week 72 visit or terminated early. This analysis will serve as the basis for submission of a marketing authorization application under regulatory provisions of accelerated/conditional approval.
- **Clinically-Based phase**:

All 2000 subjects planned to be randomized into this study will receive Aramchol or matching placebo until End-of-Study (EoS) which will occur at the time when a total of 380 subjects will experience at least 1 pre-specified clinical event or at 5 years from last subject's randomization, whichever comes first.

Extension study: Subjects that complete 7 years in the study or that are ongoing at EoS will be provided the option to receive Aramchol treatment in an open-label extension. The extension study will be detailed under a separate protocol

[redacted]

[redacted]

[redacted]

[redacted]

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6 STUDY POPULATION

The Randomized, Double-Blind, Placebo-Controlled Part will enroll adult subjects, 18–75 years old, with NASH and fibrosis (F2-F3) confirmed by liver histology who are overweight or obese and have prediabetes or type 2 diabetes.

The Open-Label Part intends to assess the safety, PK and treatment response kinetics of Aramchol 300mg BID in a broader population, including subjects with fibrosis stage 1, subjects who are not overweight, and subjects who do not have T2DM.

In both study parts, patients with cirrhosis, abnormal synthetic liver function and history or presence of decompensated liver disease will not be enrolled to the study.

6.1 Inclusion Criteria

The inclusion criteria for the Open-Label Part are the same as those of the Randomized, Double-Blind, Placebo-Controlled Part with the exception of fibrosis stage (the Open-Label Part allows enrollment of subjects with fibrosis stage 1), weight (the Open-Label Part allows enrollment of subjects who are not overweight) and Type-2 diabetes mellitus (the Open-Label Part allows enrollment of subjects who are not prediabetic or subjects who do not have Type-2 diabetes mellitus

In order to be eligible to the study, subjects must meet all the following criteria:

1. Male or female age 18 to 75 years (inclusive at first Screening visit)
2. Histological confirmation of NASH on a diagnostic liver biopsy by central reading of the slides
   - [redacted]
   - [redacted]
3. Total NAS Score 4 or more with at least 1 in each component of the NAS Score (steatosis ≥1 AND inflammation ≥1 AND ballooning ≥1)
4. Fibrosis Stage must be 2 or 3
   - Open-Label Part only: 30 subjects with fibrosis stage 1 may be included
5. [redacted]
6. Body mass index (BMI)
   - Open-Label Part: ≤ 40 kg/m^2
   - Randomized, Double-Blind, Placebo-Controlled Part: between 25kg/m^2 and 40 kg/m^2

7. [redacted]
8. Randomized, Double-Blind, Placebo-Controlled Part only: Type 2 diabetes mellitus or prediabetes: Type 2 diabetes diagnosis must be established and documented prior to screening. For prediabetes, unless pharmacologically treated, the diagnosis should be verified by screening results (by central lab) according to the American Diabetes Association criteria, which requires at least one of the following 3 criteria:
   - [redacted]
   - [redacted]
   - [redacted]
9. For subjects with type 2 diabetes, glycemia must be controlled [redacted]
10. Negative blood pregnancy test at study entry for females of childbearing potential confirmed by central laboratory
11. [redacted]
12. Able to understand the nature of the study and to provide signature of the written informed consent.

6.2 Exclusion Criteria

All exclusion criteria for the Open-Label Part are the same as those of the Randomized, Double-Blind, Placebo-Controlled Part.

Subjects will be excluded from participating in this study if they meet any of the following criteria:

1. Histologically documented liver cirrhosis (fibrosis stage 4)
2. Inability or unwillingness to undergo a liver biopsy
3. Abnormal synthetic liver function
   - [redacted]
4. ALT or AST > 5× upper limit of normal (ULN); according to central laboratory
5. Platelet count < 150,000mm^3
6. Alkaline phosphatase ≥2× ULN
7. Known or suspected hepatocellular carcinoma (HCC)
8. Model for End-Stage Liver Disease (MELD) score > 12 using OPTN formula
9. Prior history of/or planned liver transplantation
10. Prior history or presence of decompensated liver disease
11. [redacted]
12. Other (acute or chronic) coexisting liver disease based on medical history and/ or centralized review of liver histology [redacted]

13. Known alcohol and/or any other drug abuse or dependence in the last five years
    - [redacted]

[redacted]

17. Weight loss of more than 5% within 3 months prior to screening
18. History of bariatric surgery within 5 years of liver biopsy or planned surgery for weight reduction
19. Treatment with drugs that may cause NAFLD within 12 months prior to the biopsy [redacted]

[redacted]

25. Current or planned treatment with immunosuppressive drugs (e.g. adalimumab, azathioprine and methotrexate)
26. Evidence of any other unstable or untreated clinically significant hepatic, cardiovascular (including any clinically significant cardiovascular events within 3 months before screening), pulmonary, immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic or psychiatric disease
    - [redacted]

[redacted]

27. History or presence of any disease or condition known to interfere with the absorption, distribution, metabolism or excretion of drugs including bile salt metabolism (e.g.

inflammatory bowel disease (IBD); major previous or planned intestinal operation (ileal or involving the right colon); chronic pancreatitis; celiac disease or previous vagotomy)

[redacted]

29. Uncontrolled hypertension

- [redacted]

[redacted]

38. Any other condition that in the opinion of the Investigator warrants exclusion from the study

39. [redacted]

7 CONCOMITANT MEDICATIONS AND SPECIAL WARNINGS

7.1 Allowed Concomitant Medications During the Study

Any medications, excluding those mentioned in Section 7.2 may be given concomitantly as needed for the subject's welfare. Administration of all medications, including indication, dose, start and end date including dose modification, frequency, and route of administration will be recorded in the source documentation file and in the electronic Case Report Form (eCRF). Concomitant medications will be discussed and documented at each visit.

- Local (including injection, topical and inhaled) steroids are allowed

7.2 Disallowed Concomitant Medications During the Study

Investigational products are disallowed during the study.

Alternative treatments should not be initiated during study.

Drugs that are approved for the treatment of NASH (in the event that drugs are approved during the course of the study) are disallowed during the study. Therefore, subjects initiating such drugs should be discontinued from the study. A liver biopsy is recommended at end of study unless there is an available biopsy within the past 6 months.

If during the study any approved medication is started to treat NASH, the indication must be properly documented on the eCRF.

The following medications if required (and no alternative exists), will need to be discussed with the Sponsor:

- Drugs that may cause NAFLD (e.g. valproic acid, tamoxifen, methotrexate, amiodarone, chronic treatment with corticosteroids, high dose estrogen and tetracycline)
- Glucagon-like peptide-1 (GLP-1) receptor agonists
- Thiazolidinediones (TZDs)
- Vitamin E

7.3 Drug-Drug Interactions

A study in healthy subjects has shown no evidence of an interaction between Aramchol 300mg BID and the probe CYP3A4 substrate midazolam or atorvastatin which is also metabolized by this isozyme.

The potential for an effect of Aramchol on the anticoagulant activity of warfarin has not been studied; in light of its low therapeutic index, subjects receiving warfarin should have their INR monitored closely during the first few weeks of treatment with study drug.

The effects of strong inducers of CYP3A4 on concentrations of Aramchol have not been studied. **To ensure adequate exposure to Aramchol, co-administration of enzyme inducers such as rifampicin, carbamazepine, phenytoin, enzalutamide and St. John's wort should be avoided.**

For a detailed description of DDI assessment and studies refer to the current IB.

7.4 Special Warnings and Precautions for Use

7.4.1 Hepatic Impairment

Subjects with cirrhosis, abnormal synthetic liver function and history or presence of decompensated liver disease will not be enrolled to the study. Liver function tests will be monitored during treatment and criteria for discontinuing treatment should be followed (see Stopping Rules, Section 7.5.2 and 7.5.3)

7.4.2 Renal Impairment

Subjects with renal dysfunction with eGFR < 45 ml/min using the MDRD formula will not be enrolled to the study. GFR will be monitored during treatment and discontinuation may be required.

For a detailed description of special warnings and precautions refer to the current IB.

7.5 Stopping Criteria

A subject may discontinue participation in the study at any time for any reason (e.g., AE, consent withdrawal). The Investigator and/or Sponsor can withdraw a subject from the study at any time for any reason (e.g., protocol deviation, noncompliance, AE).

7.5.1 Pregnancy

Currently available data from non-clinical studies is not sufficient to rule out a potential risk on pregnancy and adequate and well-controlled studies have not been conducted in pregnant or breastfeeding women to inform drug-associated risks. Furthermore, the study may require procedures that are associated with heightened risks in pregnancy (i.e. biopsy). Hence, **pregnancy should be avoided during study and 1 month after treatment discontinuation**.

Any subject who becomes pregnant during the study must not receive additional doses of the study drug and will be withdrawn from the study.

All females of childbearing potential should practice a highly effective method of reliable contraception at least 1 month prior to randomization, throughout the study period and for 1 month after treatment discontinuation.

A woman is considered of childbearing potential if fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

[redacted]

For detailed description of non-clinical reproduction toxicity studies refer to the current IB.

7.5.2 DILI Monitoring and Stopping Rules

Hepatocellular and cholestatic DILI should be monitored during the study and subjects should be educated to recognize symptoms and seek immediate medical care.

When the Investigator or site personnel, or the Medical Monitor becomes aware of a case of suspected DILI, or discontinuation due to suspected DILI, all relevant parties (Investigator, Medical Monitor, Sponsor) are to be notified immediately.

7.5.2.1 Hepatocellular DILI:

Guidelines refer to subjects with Normal Baseline transaminase and subjects with Elevated Baseline transaminase.

Definition of Baseline transaminase (ALT and AST):

- Baseline value is the average of values from screening and baseline visits (from the central laboratory)

A subject is defined to have an Elevated Baseline when the average values from screening and baseline visits of either ALT and/or AST are ≥1.5 x ULN

[redacted]

*A “new baseline”: Transaminase levels might decline during the study. If the average transaminase value from the two visits prior to the suspected DILI event is lower than the original elevated baseline value (average from screening and baseline visits), this value should be set as the new baseline. If the new baseline is within the normal range, guidelines for normal baseline values should be followed.

For subjects under close observation, liver tests should be repeated within 2-5 days and an assessment for hepatic symptoms should be performed. The frequency of subsequent testing (weekly or biweekly) should be determined based on the subject’s clinical condition.

If close monitoring is not possible, study drug should be discontinued.

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

7.5.2.1.1 DILI Workup

Confirmation

An increase of serum ALT or AST to >3xULN (if normal at baseline) or increase in serum ALT or AST to ≥2x baseline (if abnormal at baseline) should be followed by repeat testing within 48 to 72 hours of ALT, AST, ALP, TBL, CPK and INR to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Blood samples for Aramchol PK should also be obtained.

[redacted]

- If close monitoring is not possible, study drug should be immediately discontinued.

Close Observation

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin). In case of discontinuation, study drug can be restarted only if another etiology is identified and liver enzymes have returned to normal levels.

If after re-challenge, a subject experiences DILI (i.e., recurrent elevations of total bilirubin, ALT, or AST), irrespective of the magnitude of liver enzymes elevation, the study drug should be discontinued permanently.

7.5.2.2 Cholestatic DILI

Table 1: Monitoring and stopping rules for cholestatic DILI

EVENT	ALT/AST levels	TOTAL BILIRUBIN	ACTION
Doubling of conjugated or direct bilirubin (CB or DB) - within normal values	Mild elevations*	Mild elevations*	Perform close monitoring
Doubling of conjugated or direct bilirubin (CB or DB) – above normal values	Mild elevations*	Mild elevations*	Interrupt the treatment, closely monitor the patient and initiate potential DILI evaluation. Treatment can only be initiated if an alternate etiology for liver enzyme elevation is established.
ALP/GGT ≥ 2xULN (for normal baseline)			Perform close monitoring

EVENT	ALT/AST levels	TOTAL BILIRUBIN	ACTION
ALP/GGT ≥2x baseline and> ULN (for elevated baseline)			
ALP/GGT ≥ 2xULN (for normal baseline) ALP/GGT ≥2x baseline and> ULN (for elevated baseline)	Mild elevations*	Mild elevations*	Interrupt the treatment, closely monitor the patient and initiate potential DILI evaluation. Treatment can only be initiated if an alternate etiology for liver enzyme elevation is established.
Total bilirubin elevation and symptoms consistent with clinical hepatitis (right upper quadrant pain or tenderness, jaundice, rash, etc..)	Any magnitude	2 X ULN	Discontinue the treatment, closely monitor the patient and initiate potential DILI evaluation. Treatment can only be initiated if an alternate etiology for liver enzyme elevation is established. If no cause is found, re-challenge should not be initiated.

***** *Mild elevation refers to CTCAE grade 1:*

- ALT/AST: >ULN - 3 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal

- Total bilirubin: >ULN - 1.5 x ULN if baseline was normal; > 1 - 1.5 x baseline if baseline was abnormal

If after re-challenge, a patient experiences DILI (i.e., recurrent elevations of total bilirubin, ALT, or AST), irrespective of the magnitude of liver enzymes elevation), the study drug should be discontinued permanently.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted] 308 U/L
[redacted]	[redacted]	[redacted]

7.5.3 Stopping Rules for liver-related events

In both parts of the study abdominal US and Fibroscan are performed in order to identify subjects that may have progressed to cirrhosis.
Examination should be performed under proper fasting conditions and in good quality.
Abdominal US is performed to assess for signs of progression to cirrhosis (e.g. ascites, splenomegaly).
Fibroscan values highly suggestive of progression to cirrhosis (e.g. recommended high specificity cut-off for Fibroscan LSM ≥16kp) should be verified on a repeat scan.

It is recommended to perform liver biopsy if there is high suspicion of progression to cirrhosis based on the abdominal US or based on the following assessments (confirmed through repeat testing within one month of initial testing): Fibroscan results and platelet count <150,000 mm^3 and one serum fibrosis marker indicative of cirrhosis (for example, FibroTest> 0.75 or ELF > 11.3 or FIB 4> 2.67 or NAFLD Fibrosis Score >0.676).

[redacted]

[redacted]

8 STUDY CONDUCT

8.1 Study Period

Open-Label Part:

- **Screening:** up to 8 weeks
- **Treatment period:** The Open-Label Part will continue for the same duration than the Randomized, Double-Blind, Placebo-Controlled Part. All subjects in the Open-Label Part will receive Aramchol 300mg BID until EoS.

Randomized, Double-Blind, Placebo-Controlled Part:

Screening: up to 8 weeks.

Treatment period: Subjects will remain on the same treatment assignment for up to 7 years.

End-of-Study: All 2000 subjects planned to be randomized into this study will receive Aramchol or matching placebo until EoS which will occur at the time when a total of 380 subjects will experience at least 1 pre-specified clinical event or at 5 years from last subject's randomization, whichever comes first.

Both study parts (Open Label Part and Randomized, Double Blind, Placebo Controlled Part):

Study Visits: All subjects will attend the following visits: Screening, Baseline, weeks 4, 8, 12, and every 12 weeks thereafter.

Visit scheduling for subjects who switch from the Randomized, Double-Blind, Placebo-Controlled Part to the Open-Label Part is dependent on prior exposure to Aramchol. Subjects that received active treatment will continue based on scheduled visits. Subjects that received placebo will start the scheduled visits from a Baseline visit

At the visit when the switch is performed, subjects will sign a new ICF and complete activities as applicable (e.g. laboratory, imaging, stool samples).

Early discontinuation

There are two types of early discontinuation:

- **Early Treatment Discontinuation (ETD)**: Subject discontinues treatment but continues with the scheduled visits.
- **Early Study Discontinuation (ESD)**: Subject discontinues study.

[redacted]

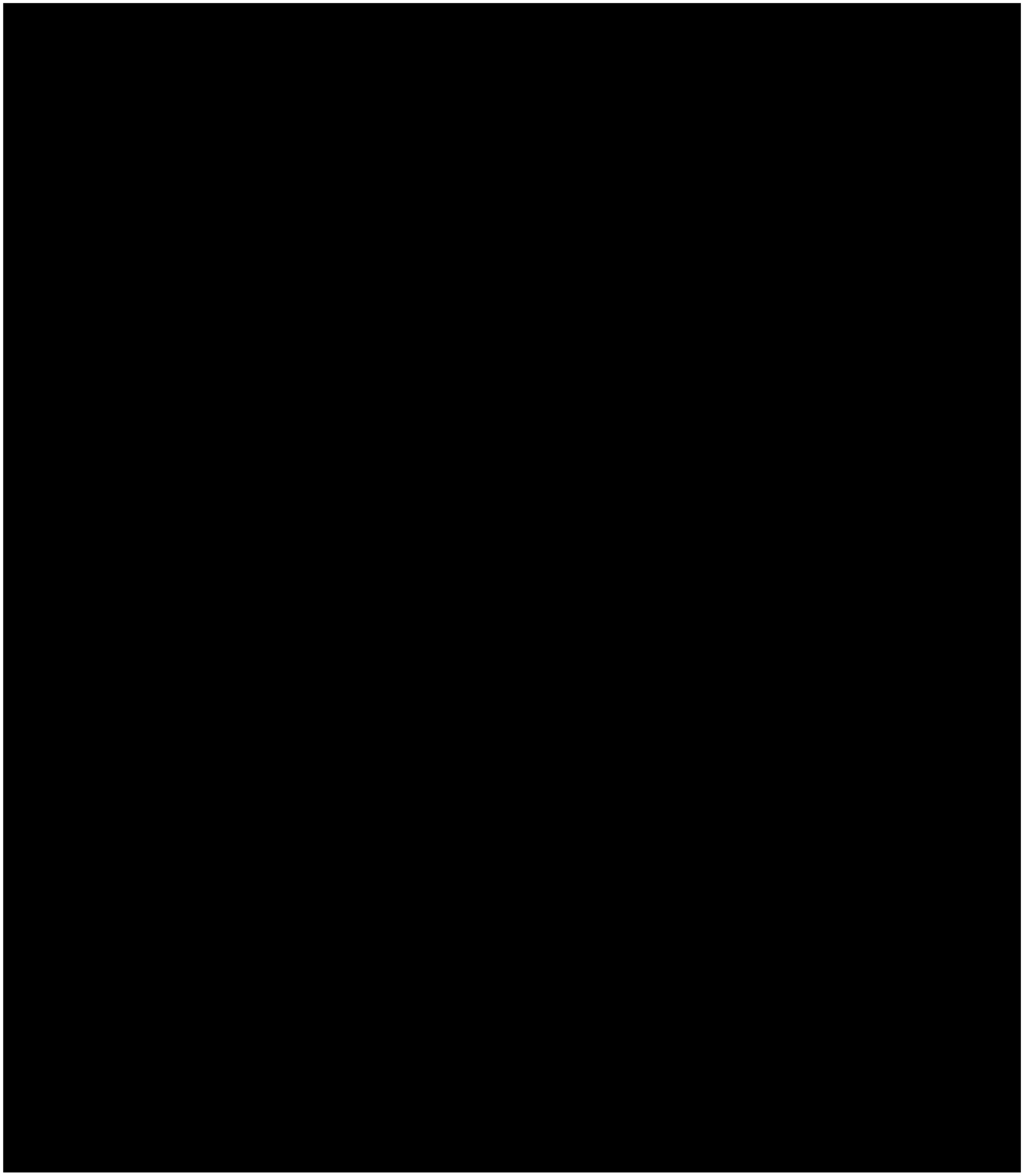
<u>Randomized, Double-Blind, Placebo-Controlled Part</u>:

- **Week 72 biopsy**: may be performed from 2 weeks prior to week 72 visit and up to 6 weeks after week 72
- **5-year biopsy**: may be performed at the 5-year visit± 8 weeks

[redacted]

[redacted]

[redacted]



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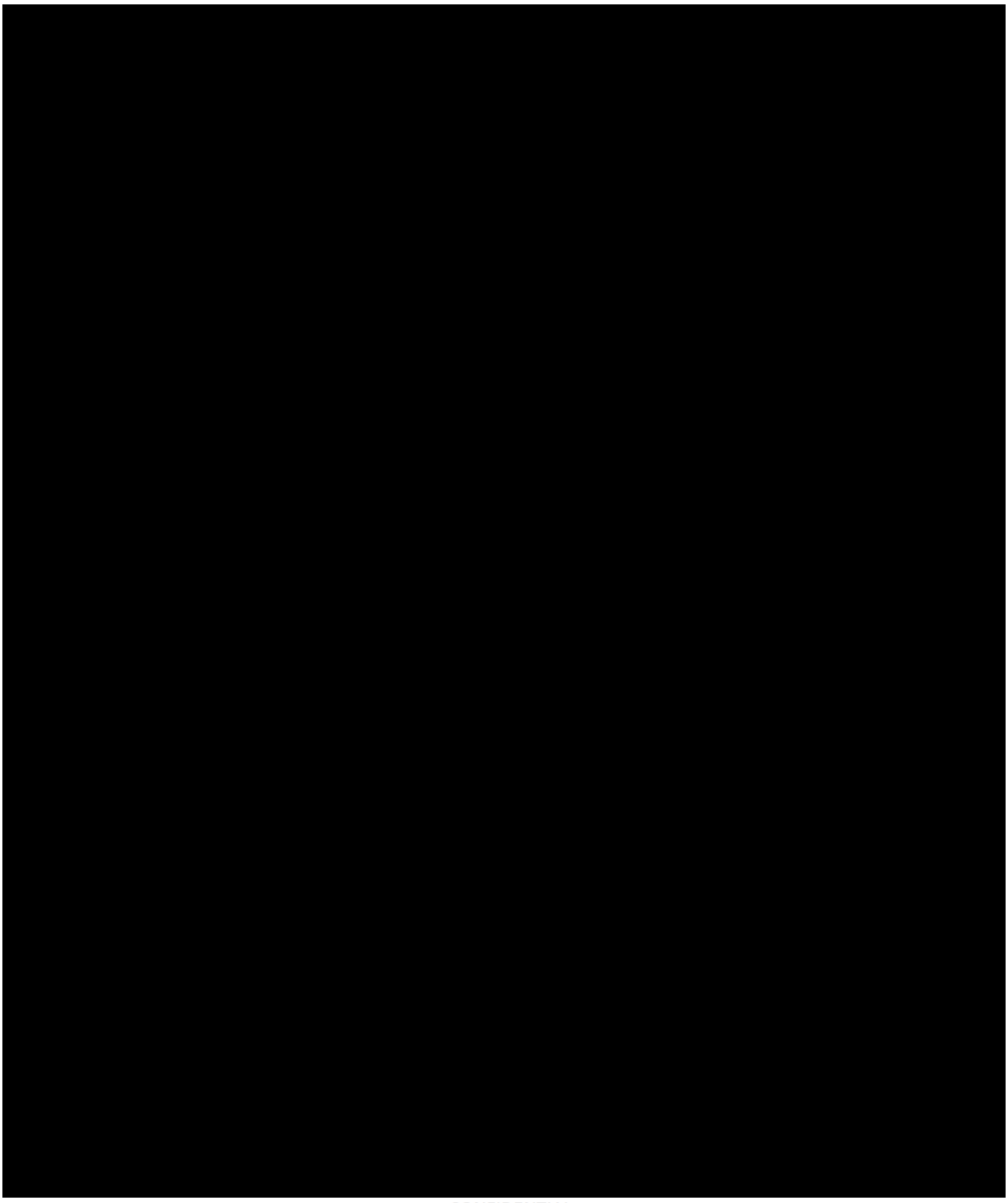

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8.2.1 Screening Period

The procedures should proceed in the following order:

- **Informed consent**: Prior to performing any study activities/evaluations, the subject must be thoroughly informed about all aspects of the study, including the study design with a Histology-Based endpoint that may serve as the basis for submission of a marketing authorization application and continuation with the same treatment assignment to a Clinically-Based endpoint, scheduled study visits at the clinical site, telephone contacts and all activities. The subject will also be informed about the importance of remaining in the study even if study medication is discontinued. The written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent process. A separate consent form will be signed for the blood sample, which will be taken for genetic parameters. Signed copies of the informed consent forms should be given to the subject.
- Subjects who switch from the Randomized, Double-Blind, Placebo-Controlled Part to the Open-Label Part are required to sign a new ICF.
- **Screening number allocation:** a unique screening number will be allocated to any subject who signed ICF using the Randomization and Trial Supply Management (RTSM) system.
- The following will be assessed/performed:
    - Demographics
    - Alcohol and smoking status
    - Medical history
    - Liver disease history including prior treatment (disease onset, previous biopsy, prior treatment for NASH, participation in other NASH clinical studies)
    - Concomitant medications
    - Dietary and lifestyle habits as well as physical activity regimen (discussion and counseling about importance of diet, weight management and exercise)
    - Physical examination
    - Body measurements including height, weight, waist circumference
    - Vital signs including blood pressure, heart rate, respiratory rate, and temperature
    - Electrocardiogram (ECG)
    - Laboratory samples

      Fasting (8 hours) is required before the visit
        - Complete blood count, Serum biochemistry, Serology (HBV, HCV and HIV), Thyroid function (TSH, T3 and T4), Renal function (creatinine and eGFR), CPK, Coagulation, Glycemic parameters, Urinalysis, Serum β-hCG in women of childbearing potential
        - MELD will be calculated

    - Blood samples for potential biomarkers (including but not limited to ProC3 and ELF), metabolomics and better understanding of the mechanism of action will be collected.
- Abdominal ultrasound (US) to assess the right upper quadrant (RUQ) for hepatocellular carcinoma (HCC), cholelithiasis, choledocholithiasis, cholecystitis, or presence of other hepatic abnormalities as well as signs of cirrhosis (e.g. ascites, splenomegaly). US done in the 3 months prior to screening is acceptable.
- Fibroscan) should be performed under proper fasting and in good quality. Fibroscan in the 4 weeks prior to screening is acceptable.
- Liver biopsy
    - Biopsy should be performed as the final eligibility assessment step and only after all previous eligibility criteria were confirmed.
        - Open-Label Part: Biopsies performed in the 9 months prior to randomization are acceptable and will be sent for central reading.
        - Randomized, Double-Blind, Placebo-Controlled Part: Biopsies performed in the 6 months prior to randomization are acceptable and will be sent for central reading
    - Slides will be evaluated by central pathology reading
    - Coagulation results should be within normal ranges before the biopsy is performed. If the subject is taking any anticoagulant it should be discontinued a sufficient amount of time before the biopsy to avoid any undue bleeding. Non-steroidal anti-inflammatory drugs (NSAIDs) are prohibited for 48 hours prior to the biopsy.
- The subject will be requested to report any AE starting at ICF signature date.
- Any new clinically significant physical, clinical or laboratory parameters observed during screening must be documented as medical history. After Screening, a new, or worsening clinically significant parameter observed must be documented as an AE in the source documentation file and in the eCRF.

At the visit when the switch is performed, subjects will sign a new ICF and complete activities as applicable (e.g. laboratory, imaging, stool samples).

[redacted]

8.2.2 Baseline Visit – Randomization

- Eligibility Criteria verification (ensure no changes occurred since screening visit)
- Randomization number allocation by RTSM system

- The following should be performed/assessed during the visit:
- Physical examination
- Body measurements including weight, and waist circumference
- Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- Dietary and lifestyle changes as well as change in physical activity regimen will be assessed, and subjects will be counseled
- Concomitant medications
- Adverse Events
- ECG
- Laboratory:

  Fasting (8 hours) is required before the visit
  - A urine pregnancy test in women of childbearing potential
  - Complete blood count and serum biochemistry, Renal function (creatinine and eGFR), Coagulation, CPK, Glycemic parameters
  - MELD will be calculated using the OPTN formula/calculator (https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/)
  - Blood samples for potential biomarkers (including but not limited to ProC3 and ELF), metabolomics and better understanding of mechanism of action will be collected.
  - Blood sample for gene analysis will be taken from subjects providing consent in a dedicated ICF (subject to local regulations and approval), preferably at Baseline visit, but will be accepted at any other visit. Samples will be kept frozen for future analysis
- In the Open-Label Part: Stool samples for analysis of microbiome and better understanding of mechanism of action will be collected
- Study drug dispensing according to the kit number provided by RTSM system
- Subjects will be allocated to treatment groups during their baseline visits based on randomization list. The RTSM system will assign a unique randomization number for each subject, in addition to the screening number previously allocated.
- The first dose of study drug will be taken on site, and only after all visit activities have been performed.

Following Baseline visit, the following assessments will be performed during **scheduled visits** at Week 4, 8, 12, and every 12 weeks thereafter.

8.2.3 Open-Label Part- Scheduled visits (not including End of Study visit)

Following Baseline visit, the following assessments will be performed during scheduled visits at Week 4, 8, 12, and every 12 weeks thereafter.

The following should be performed/assessed during the visit:

- Physical examination at weeks 24 and every 24 weeks thereafter
- Body measurements including weight and waist circumference at week 12 and every visit thereafter
- Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- Dietary and lifestyle changes as well as change in physical activity regimen will be assessed, and subjects will be counseled
- Concomitant medications
- Adverse Events
- ECG
- Laboratory:
  Fasting (8 hours) is required before the visit
  - A urine pregnancy test in women of childbearing potential
  - Complete blood count and serum biochemistry will be measured at every study visit
  - Renal function (creatinine and eGFR) will be measured at every study visit
  - Coagulation at every visit
  - CPK will be measured at weeks 24 and every 24 weeks thereafter
  - Glycemic parameters: fasting glucose will be measured at every study visit. HbA1c, C-peptide, Insulin and HOMA-IR at weeks 12,24 and every 24 weeks thereafter
  - Thyroid function (TSH, T3 and T4) will be measured at week 48
  - MELD will be calculated at week 12, and at every visit thereafter
  - Blood sample for PK will be collected from week 4 until 72 weeks and every 24 weeks thereafter
  - Blood samples for potential biomarkers (including ProC3 and ELF), metabolomics and better understanding of mechanism of action will be collected at week 12, 24 ,48 and every 24 weeks thereafter
  - Stool samples for analysis of microbiome and better understanding of mechanism of action will be collected at weeks 4, 12, 24, 48, 72
- Drug accountability
- Study drug dispensing
- Abdominal ultrasound (US) and Fibroscan will be performed at week 24 and every 24 weeks thereafter
  - Abdominal US is performed to assess for signs of HCC or other RUQ new findings as well as signs of progression to cirrhosis (e.g. ascites, splenomegaly)
  - Fibroscan is performed as part of the NITs assessment in the study. Scan should meet the minimal quality definition (subject fasting for a minimum of 3 hours and at least 10 valid shots with IQR≤30% of the value of the median)
  - Fibroscan is also performed in order to identify subjects that may have progressed to cirrhosis. Examination should be performed under proper fasting conditions and in good quality. Values highly suggestive of progression to cirrhosis (e.g. recommended high specificity cut-off for Fibroscan LSM ≥16kp) should be verified on a repeat scan.

It is recommended to perform liver biopsy if there is high suspicion of progression to cirrhosis based on the abdominal US or based on the following assessments (confirmed through repeat testing within one month of initial testing): Fibroscan results and platelet count <150,000 mm^3 and one serum fibrosis marker indicative of cirrhosis (for example, FibroTest> 0.75 or ELF > 11.3 or FIB 4> 2.67 or NAFLD Fibrosis Score >0.676).

- **Liver Biopsy:**
  - The 2nd scheduled liver biopsy will be performed based on randomization groups A, B, C at week 24 or 48 or 72, respectively.
    The biopsy may be performed from 2 weeks prior to the scheduled biopsy up to 6 weeks after the scheduled biopsy
  - A 2nd post-baseline liver biopsy sample will be collected for subjects whose post baseline liver biopsy at week 24 or 48 or 72 does not show at least 1 stage improvement in fibrosis (fibrosis non-responders). The 2nd post-baseline liver biopsy sample will be collected 1 year later (i.e. at weeks 72 or 96 or 120 respectively)

Coagulation results should be within normal ranges before the biopsy is performed. If the study subject is taking any anticoagulant it should be discontinued a sufficient amount of time before the biopsy to avoid any undue bleeding. NSAIDs are prohibited 48 hours prior to the biopsy

8.2.4 Open-Label Part - End-of-Study Visit

Subjects who are still in the study at the time the Sponsor announced EoS will be requested to attend this visit.

The following should be performed/reviewed during the visit:

- Physical examination
- Vital signs including blood pressure, heart rate, respiratory rate and temperature
- Body measurements including weight and waist circumference
- Concomitant medications
- Adverse Events
- ECG
- Dietary and lifestyle changes as well as change in physical activity regimen will be assessed, and subjects will be counseled
- Laboratory:
  Fasting (8 hours) is required before the visit
  - A urine pregnancy test in women of childbearing potential
  - Complete blood count and serum biochemistry, Renal function (creatinine and eGFR), Coagulation, Thyroid function (TSH, T3 and T4), CPK, Glycemic parameters
  - Blood sample for PK will be collected

- Blood samples for potential biomarkers, metabolomics and better understanding of mechanism of action
- Drug accountability

8.2.5 Randomized, Double-Blind, Placebo-Controlled Part Scheduled visits (not including End of Study visit)

Following the Baseline visit, the following assessments will be performed during scheduled visits at Week 4, 8, 12, and every 12 weeks thereafter.

The following should be performed/assessed during the visit:

- Physical examination at weeks 24 and every 24 weeks thereafter
- Body measurements including weight and waist circumference at week 12 and every visit thereafter
- Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- Dietary and lifestyle changes as well as change in physical activity regimen will be assessed, and subjects will be counseled
- Concomitant medications
- Adverse Events
- ECG
- Laboratory:
  Fasting (8 hours) is required before the visit
  - A urine pregnancy test in women of childbearing potential
  - Complete blood count and serum biochemistry will be measured at every study visit
  - Renal function (creatinine and eGFR) will be measured at every study visit
  - Coagulation at every visit
  - CPK will be measured at weeks 24 and every 24 weeks thereafter
  - Glycemic parameters: fasting glucose will be measured at every study visit. HbA1c, C-peptide, Insulin and HOMA-IR at weeks 12,24 and every 24 weeks thereafter
  - Thyroid function (TSH, T3 and T4) will be measured at week 48
  - MELD will be calculated at week 12, and at every visit thereafter
  - Blood sample for PK will be collected from week 4 until 72 weeks and every 24 weeks thereafter
  - Blood samples for potential biomarkers (including ProC3 and ELF), metabolomics and better understanding of mechanism of action will be collected at week 12 24, 48 and every 24 weeks thereafter
- Drug accountability
- Study drug dispensing
- Abdominal ultrasound (US) and Fibroscan will be performed at week 24 and every 24 weeks thereafter
  - Abdominal US is performed to assess for signs of HCC or other RUQ new findings as well as signs of progression to cirrhosis (e.g. ascites, splenomegaly)

- Fibroscan is performed as part of the NITs assessment in the study. Scan should meet the minimal quality definition (subject fasting for a minimum of 3 hours and at least 10 valid shots with IQR≤30% of the value of the median)
- Fibroscan is also performed in order to identify subjects that may have progressed to cirrhosis. Examination should be performed under proper fasting conditions and in good quality. Values highly suggestive of progression to cirrhosis (e.g. recommended high specificity cut-off for Fibroscan LSM ≥16kp) should be verified on a repeat scan.

  It is recommended to perform liver biopsy if there is high suspicion of progression to cirrhosis based on the abdominal US or based on the following assessments (confirmed through repeat testing within one month of initial testing): Fibroscan results and platelet count <150,000 mm^3 and one serum fibrosis marker indicative of cirrhosis (for example, FibroTest> 0.75 or ELF > 11.3 or FIB 4> 2.67 or NAFLD Fibrosis Score >0.676).

- **Liver biopsy**:
  - 72-week liver biopsy may be performed from 2 weeks prior to the week 72 visit and up to 6 weeks after week 72.
  - 5-year liver biopsy should occur within 8 weeks (prior to or after) of the 5-year visit, unless there is an available biopsy within the past year.

  Coagulation results should be within normal ranges before the biopsy is performed. If the study subject is taking any anticoagulant it should be discontinued a sufficient amount of time before the biopsy to avoid any undue bleeding. NSAIDs are prohibited 48 hours prior to the biopsy.

8.2.6 Randomized, Double-Blind, Placebo-Controlled Part: End-of-Study Visit and 7-Year Visit

Subjects that complete 7 years in the study or that are ongoing at the time the Sponsor announced EoS will be requested to attend this visit and will be provided the option to receive Aramchol treatment in an open-labeled extension. The extension study will be detailed under a separate protocol.

The following should be performed/reviewed during the visit:

- Physical examination
- Vital signs including blood pressure, heart rate, respiratory rate and temperature
- Body measurements including weight and waist circumference
- Concomitant medications
- Adverse Events
- ECG
- Dietary and lifestyle changes as well as change in physical activity regimen will be assessed, and subjects will be counseled

- Laboratory:

Fasting (8 hours) is required before the visit

  - A urine pregnancy test in women of childbearing potential
  - Complete blood count and serum biochemistry, Renal function (creatinine and eGFR), Coagulation, Thyroid function (TSH, T3 and T4), CPK, Glycemic parameters
  - Blood sample for PK will be collected
  - Blood samples for potential biomarkers, metabolomics and better understanding of mechanism of action

- Drug accountability
- Liver biopsy will be conducted as follows
  - In case the Sponsor announces EoS and the subject has not reached 5-year visit, it is recommended to perform a liver biopsy, unless there is an available biopsy within the past year.
  - There is no scheduled biopsy at year 7 visit

  Coagulation results should be within normal ranges before the biopsy is performed. If the study subject is taking any anticoagulant it should be discontinued a sufficient amount of time before the biopsy to avoid any undue bleeding. NSAIDs are prohibited 48 hours prior to the biopsy.

[redacted]

8.2.8 Early Discontinuation Visit - ETD/ESD (both study parts; Open-Label Part and Randomized, Double Blind, Placebo-Controlled Part)

There are two types of discontinuation in the study: treatment discontinuation (i.e. early **treatment** discontinuation) and study withdrawal (i.e. early **study** discontinuation).

All efforts should be made for subjects to continue participation in the study, even in case treatment is discontinued. This includes also subjects who discontinue treatment due to Stopping Rules for Liver-Related Events including progression to cirrhosis.

For any subject that stops study treatment, it should be explained that they can complete all future study visits and remain in the study without taking the study drug. Subjects will perform discontinuation procedures and will attend future study visits according to schedule, without dispensing of study drug. If they do not choose to complete all scheduled study visits, subjects will be provided the option of less frequent visits and/or telephone contact for collection of critical outcome assessment. At a minimum, additional options for annual follow-up and permission to access the subject's electronic/medical records for follow-up information should be offered.

The reason for early discontinuation will be recorded on the relevant eCRF (ETD or ESD).

Since it is expected that a subject may discontinue treatment, continue follow up but later withdraw from the study, both an ETD and an ESD visit may be performed and the corresponding reason should be recorded for each.

A subject may withdraw or be withdrawn from treatment/study for the following reasons:

- Withdrawal by subject
    - This category may be used for any personal reasons not related to safety or lack of efficacy for NASH or to study drug
    - A subject may withdraw consent from treatment but continue follow up in the study. Withdrawal from the study is defined as subject withdrawal of consent to contribute any additional information
- Physician Decision
- Protocol Deviation
- Adverse Event
- Lack of efficacy for NASH
    - Lack of efficacy should be defined carefully after ruling out withdrawal of consent for personal reasons
- Pregnancy
- Protocol-Specified Stopping rule for Liver-Related Events (Section 7.5.3)
- Lost to follow-up
- Study Terminated by Sponsor
- Death
- Other

Refusal to perform a scheduled biopsy will not result in withdrawal from treatment/study.

A discontinuation visit should be performed for all subjects who prematurely discontinue treatment which includes both ETD (early treatment discontinuation) and ESD (early study discontinuation).

Discontinuation visit will be performed as soon as possible after the last study dose.

Subjects who discontinue from the study (ESD) will perform discontinuation procedures and end their participation in the study.

In the following cases the subject will be discontinued from the study (ESD will be required): pregnancy, a subject that was unblinded due to emergency (Section 8.4.4) and a subject that receives an approved treatment for NASH (in the event that drugs are approved during the course of the study).

Early discontinuation visits (ETD or ESD) will include the following:

- Physical examination
- Vital signs including blood pressure, heart rate, respiratory rate and temperature
- Body measurements including weight and waist circumference
- Concomitant medications
- Adverse events
- ECG
- Dietary and lifestyle changes as well as change in physical activity regimen will be assessed, and subjects will be counseled
- Laboratory:

  Fasting (8 hours) is required before the visit
  - A urine pregnancy test in women of childbearing potential
  - Complete blood count and serum biochemistry, Renal function (creatinine and eGFR), Coagulation, Thyroid function (TSH, T3 and T4), CPK, Glycemic parameters
  - MELD will be calculated
  - Blood sample for PK will be collected
  - Blood samples for potential biomarkers (including ProC3 and ELF), metabolomics and better understanding of mechanism of action
- In the Open-Label Part, stool samples will be collected if early discontinuation is prior to week 72.

  Drug accountability
- **Liver biopsy at early discontinuation**: For subjects who discontinue treatment but remain in the study and continue to be followed, conduct a liver biopsy either at the treatment discontinuation visit or, if consented by the subject, during the regularly scheduled study visits.

  Open-Label Part: It is recommended to perform a liver biopsy in a subject that discontinues treatment between week 24 to week 72 unless the scheduled biopsy has already been performed.

Randomized, Double-Blind, Placebo-Controlled Part:

- It is recommended to perform a liver biopsy in a subject that discontinues treatment between week 24 to week 72 unless there is an available biopsy within the past 6 months.
- It is recommended to perform a liver biopsy in a subject that discontinues treatment between 2-years to 5-years, unless there is an available biopsy within the past 6 months.

[redacted]

8.4 Investigational Medicinal Products/Study Drugs

8.4.1 Treatment Administration

Open-Label Part: Aramchol 300mg will be taken twice daily (BID).

Randomized, Double-Blind, Placebo-Controlled Part: Aramchol 300mg or matching placebo will be taken twice daily (BID).

Two tablets should be taken by mouth daily, one after breakfast in the morning and the other after a meal in the evening.

8.4.2 Method of Assigning Subjects to Treatment Groups

Open-Label Part:

Subjects, including those already randomized to Aramchol 300mg BID or Placebo, will be randomized in a ratio of 1:1:1 to receive Aramchol 300mg BID according to the below grouping:

- Group A: The post-baseline liver biopsy will be conducted at week 24
- Group B: The post-baseline liver biopsy will be conducted at week 48
- Group C: The post-baseline liver biopsy will be conducted at week 72

Randomization in the Open-Label Part will employ a semi-minimization algorithm to balance the 3 groups in number of subjects, distribution of subjects according to fibrosis score (F1, F2 and F3), presence or absence of T2DM, and prior exposure to Aramchol 300mg BID. F1 subjects will be capped to enroll no more than 30 subjects.

Subjects already randomized and in the Randomized, Double-Blind, Placebo-Controlled Part in the selected sites participating in the Open-Label part will be given the option to switch to the Open-Label Part.

Randomization in the Open-label Part will employ a semi-minimization algorithm to balance the 3 groups in number of subjects, distribution of subjects according to fibrosis score (F1, F2 and F3), presence or absence of T2DM, and prior exposure to Aramchol 300mg BID. F1 subjects will be capped to enroll no more than 30 subjects.

Randomized, Double-Blind, Placebo-Controlled Part:
An eligible subject will randomly be allocated to treatment with Aramchol or matching placebo based on a randomization scheme employing a 2:1 assignment ratio, respectively, using permuted blocks stratified by country/geographical region (CGR) and by baseline Fibrosis stage (F2 or F3).

[redacted]

8.4.3 Study Blinding and Blinding Plan

Open-Label Part:
All subjects will receive Aramchol 300mg BID.

Randomized, Double-Blind, Placebo-Controlled Part:
Aramchol 300mg BID or matching placebo will be administered in a blinded manner. To maintain the blind, Aramchol and matching placebo capsules will have identical appearance and will be packaged in identical bottles.

Participating subjects, Investigators, the Sponsor and any personnel involved in subjects' assessments, monitoring, analysis and Data Management will be kept blinded to the treatment assignment, excluding the designated personnel in clinical supply vendor and the RTSM vendor.

All liver biopsies will be centrally evaluated while the assessor is blinded to treatment assignment as well as to other parameters including site and sequence or indication (screening biopsy or week 72 biopsy or biopsy due to suspicion to progression to cirrhosis).

Adjudication committee members will be blinded to treatment assignment.

The DMC will consist of independent physicians with expertise in liver disease and internal medicine and an independent biostatistician, all with prior experience and expertise in clinical trials. An Independent Unblinded Statistician will prepare the reports for review by the DMC.

Unblinded safety reports if required for regulatory submissions as well as reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) will be handled by dedicated personnel. For these purposes, unblinding will be performed on an individual subject's basis. The Sponsor will remain blinded to that individual subject's treatment assignment.

In case of emergency code breaking, when the study drug assignment is needed to make treatment decisions for the subject, the Investigator may unblind the subject's drug assignment. The unblinded subject will be withdrawn from the study. In such cases of emergency unblinding, subject's treatment assignment will not be revealed to the Sponsor.

Analysis of the Histology-Based primary endpoint will be conducted when 1000 subjects complete their initial treatment period of 72 weeks (or terminated earlier). For the purpose of the conduct of these analyses which may be followed by a marketing authorization application, the Sponsor will establish a special taskforce firewalled from the study team. The taskforce will be led by a Sponsor management team member not directly involved in the ongoing management of the study. To maintain the integrity of the final post-Week 72 analyses, only a minimal number of personnel belonging to this taskforce will be exposed to the subject -level data, primarily to facilitate regulatory filings and required public disclosures.

Furthermore, study subjects, Investigators, and the Sponsor personnel involved in the ongoing study management and any personnel involved in subjects' assessments, monitoring, and Data Management will remain blinded to treatment assignment.

Following the conduct of the Histology-Based milestone analyses, major findings may be publicly disseminated by the Sponsor in accordance with 21 CFR 312.7. To preserve study blinding, trial integrity, subject's adherence and retention, only grouped level summary of results of the Histology-Based analyses including key secondary as well as potentially exploratory endpoints planned to be analyzed at this study milestone will be disseminated. Summary safety findings will also be disseminated.

Study integrity and blinding will not be compromised by the public dissemination of information due to the following major reasons: 1) the individual subject treatment assignment and data listings will only be shared with the Sponsor's dedicated taskforce and with regulatory authorities. 2) The publicly disseminated information will be on a "by group" basis. 3) The observed proportions of Histology-Based outcomes will not allow determining individual subject assignment. 4) The observed proportions of adverse events will not allow determining individual subject assignment.

A more detailed Statistical Analysis Plan (SAP) covering the analyses of the Histology-Based data as well as the Clinically-Based data at EoS was submitted prior to study initiation. SAP amendment will also be prepared and submitted prior to revealing of the blind for the analysis of the Histology-Based data.

8.4.4 Emergency Code Breaking

Open-Label Part: Not applicable since all subjects will receive Aramchol 300mg BID.

Randomized, Double-Blind, Placebo-Controlled Part:
In case of any emergency as per the Investigator criteria or pregnancy, **when the study drug assignment is needed to make treatment decisions for the subject**, the Investigator may unblind the subject's drug assignment. The unblinded subject will be withdrawn from the study. The subject should remain in the study for follow-up until resolution or stabilization of the event.

Unblinding is performed in the Interactive Web Response System (IWRS). The process includes the following steps:

- Confirming the identity of the subject
- Confirming the unblinding request
- Entering the unblinding reason
- Entering a password

[redacted]

[redacted]

[redacted]

8.5 COVID-19 Contingency measures

8.5.1 General

Due to the COVID-19 pandemic the study subject may be either not allowed or unwilling to attend a regularly scheduled study visit or the visit may otherwise not be able to take place at the study site per standard practice. In that case contingency measures described in Sections 8.5.2 through 8.5.8 may potentially be applied according to the following general guidance:

- Local regulations and ordinances pertaining to the COVID-19 pandemic must always be followed and the safety of study subjects and research team must be assured.
- Every effort must be made to complete the full scope of the study visit activities and procedures. Any deviation from the standard practice and procedures of in person visit at the study site and use of the allowed contingency measures, must be clearly documented and flagged as COVID-19 related, and reported to the EC/IRB as applicable.
- Study subjects must be informed of any change in the study conduct that may be implemented under these contingency measures and verbal agreement documented.
- The contingency measures DO NOT APPLY to Screening and Baseline visits.
- The contingency measures specified here do not contradict any local rules or regulations

8.5.2 Alternative Location Visit

In case circumstances related to COVID-19 prevent holding the study visit at the standard site location the PI may identify an alternative location for holding the study visit (e.g. private clinic, outside of the hospital/study facility, subject home) so long as the alternative location provides an appropriate environment for a study visit (including privacy and appropriate physical conditions), the necessary equipment, including laboratory and study drug kits and personnel is available and the study subject agrees with the alternative location.

8.5.3 Interview by Phone or Video Conference

The PI may decide to hold the scheduled subject interview by phone or video conference instead of as a standard in person meeting in order to minimize the social interaction and time required for the actual physical visit. At the beginning of the interview the identification of the participants must be verified by both sides presenting themselves by full name, and the existence of proper privacy conditions for the subject must be confirmed and documented. The interview must be documented as a phone/video conference interview in the subject file.

8.5.4 Necessary data collection requirements

In order for a visit to qualify as a study visit and to allow a new drug kit to be dispensed as part of the visit, the following essential visit activities must be performed:
(a) Subject interview – including changes in health condition, adverse events, changes in medication, and confirmation of study drug intake as per instructions.
(b) Safety laboratory measurements - including all tests defined in the protocol for the specific visit, with the exception of blood draws for PK. In case the specific processing and storage requirements for PK testing cannot be assured, the visit can still qualify as a study visit even if blood for PK is not taken.

8.5.5 Study equipment and materials

Storing of study related equipment and material (i.e. documentation, study drug kits, lab specimens, lab kits, devices, etc.) outside the study site should be short term and limited to what is directly required for holding the study visit at the alternative location or subject home.

No equipment or material should be stored at the subject's home. In cases where equipment and materials are kept outside the study sites, it must be maintained securely and under the required storage conditions.

8.5.6 Study drug dispensing and used drugs bottles collection

In case study visit is performed at an alternative location, the following applies:

- Study drug dispensing must only take place in case the required data collection requirements (see Section 8.5.2) have been met.
- Allocation of study drug kit by the IRT system should be done per the standard normally followed at the study site. The allocated kit must be taken under appropriate storage conditions to the alternative location and dispensed to the subject during the study visit. A study drug kit may be delivered to the study subject by courier but must not be mailed.
- The allocated kit must be properly documented at the site as per standard practice and confirmation of delivery/receipt is documented in the subject file.
- Used study drug bottles should be collected if possible, but in case circumstances do not allow, the subject should be instructed to keep the old used bottles and return them at the earliest feasible time to the alternative location or study site. If returned to an alternative location or during in-home visits, the PI and study personnel or delegate are responsible for ensuring transport to the site and full count of returned study drug at the study site.

8.5.7 Laboratory Specimens

In case the study visit is conducted in an alternative location:

- Safety laboratory samples should be processed following standard procedure by the central laboratory if the central laboratory services are available.
- In case of disruption to the central laboratory operation or the courier service operation, processing of the laboratory samples by a local laboratory is allowed.
- Test results reported by the local laboratory should be reviewed by the PI and the results as well as the actual review of the results, should be documented in the subject file.
- Laboratory specimen collected during a visit conducted at an alternative location must follow the standard practices of maintenance, storage, shipment and documentation.

8.5.8 Additional contingency measures

In case of standard protocol-specified time windows cannot be met the following will apply:

- Screening time window will be extended to 12 weeks
- Allowable time window for the visits will be extended up to ± 14 days for visits during the first 3 months of treatment, and up to 21 days after the first 3 months of the study.

9 ASSESSMENTS & PROCEDURES

9.1 Liver Biopsy

9.1.1 Open-Label Part

Includes the following liver biopsies:

- **Baseline liver biopsy**: Performed during screening (biopsies performed in the 9 months prior to randomization are acceptable and will be sent for central reading).
- **A post-baseline scheduled liver biopsy**: Performed based on randomization groups A, B, C at week 24 or 48 or 72 respectively. The biopsy should be performed from 2 weeks prior to the scheduled biopsy and up to 6 weeks after the scheduled biopsy
    - In order to more comprehensively explore the kinetics of histological outcome measures (e.g. are there subjects who may not show improvement in outcome at week 24, 48 or 72 but may improve with longer duration of treatment), a 2nd post-baseline liver biopsy sample will be collected for subjects whose post-baseline liver biopsy at week 24 or 48 or 72 does not show at least 1 stage improvement in fibrosis (fibrosis non-responders). The 2nd post-baseline liver biopsy sample will be collected 1 year later (i.e. at weeks 72 or 96 or 120 respectively
- [redacted]

9.1.2 Randomized, Double-Blind, Placebo-Controlled Part

Includes the following scheduled liver biopsies:

- **Baseline liver biopsy**: Performed during screening (biopsies performed in the 6 months prior to randomization are acceptable and will be sent for central reading).
- **72 weeks liver biopsy:** Performed from 2 weeks prior to week 72 visit and up to 6 weeks after week 72

[redacted]

[redacted]

[redacted]

9.2 Fibroscan

Fibroscan will be performed at Screening, week 24 and every 24 weeks thereafter as at early termination/study completion.

- Screening Fibroscan: Fibroscan done in the 4 weeks prior to screening is acceptable
- Fibroscan is performed as part of the NITs assessment in the study
- Fibroscan is also used in the study as follow-up to assist in identifying subjects who might require definite diagnosis by biopsy.

Fibroscan recommendations are as follows:

[redacted]

9.3 Abdominal Ultrasound

Abdominal ultrasound will be performed at Screening, week 24 and every 24 weeks thereafter as at early termination/study completion.

- Screening US: US done in the 3 months prior to screening is acceptable
- Abdominal US should include
  - RUQ abdominal US to assess for hepatocellular carcinoma (HCC), cholelithiasis, choledocholithiasis, cholecystitis, or presence of other hepatic abnormalities. Results will be recorded on a dedicated CRF page
  - Abdominal US is performed to assess for signs of HCC or signs of progression to cirrhosis (e.g. ascites, splenomegaly)

9.4 MELD score

MELD will be calculated at screening, baseline, weeks 12, and at every study visit thereafter and at early termination/study completion.

MELD Calculation will be done using the OPTN formula/calculator which requires the input of the following lab values – Bilirubin, Sodium, Creatinine and INR.
(https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/)

9.5 Pre-Defined Clinical Outcome Events

Pre-defined clinical events for the Clinically-Based endpoint will be adjudicated by an independent adjudication committee:

- All-cause mortality
- Liver transplant
- Histological progression to cirrhosis
- MELD score >15 if baseline MELD score was <12
- Hospitalization due to hepatic decompensation event(s)
  - Hepatic encephalopathy grade ≥2 (as assessed by West Haven scale)
  - Variceal bleeding

- New onset ascites requiring treatment
- Spontaneous bacterial peritonitis as assessed by either positive cell culture or cell count

[redacted]

9.7 Pharmacokinetics

Blood sample for analysis of concentrations of Aramchol and its metabolites as well as for population PK will be collected at all study visits from week 4 until week 72 and every 24 weeks thereafter and at early termination/study completion. Subjects attending a site visit in the morning should take their dose as usual in the evening before the visit and should record the time of dosing. They should NOT take their dose on the morning of their visit until after the blood sample for PK has been drawn. Subjects attending a site visit in the afternoon should take their morning dose as usual and should record the time of dosing.

The Investigator will record the timing the subject has taken the last tablet prior to blood drawing and the time of PK sampling.

Samples will be used for pharmacokinetic endpoints analysis and safety if deemed necessary.

9.8 Biomarkers, Metabolomics Gene and Microbiome Analysis

- Blood samples for potential biomarkers (including but not limited to ProC3 and ELF), metabolomics and better understanding of mechanism of action will be collected at Screening, Baseline, weeks 12, 24, 48 and every 24 weeks thereafter and at early termination/study completion.
- Blood sample for gene analysis will be taken from subjects providing consent in a dedicated informed consent form (ICF) (subject to local regulations and approval), preferably at Baseline visit, but will be accepted at any other visit. Samples will be kept frozen for future analysis
- In the Open-Label Part, stool samples for analysis of microbiome and better understanding of mechanism of action will be collected at Baseline, weeks 4, 12, 24, 48 and 72 and at early termination (if prior to week 72).

9.9 SAFETY ASSESSMENTS

9.9.1 Adverse Events

AEs will be recorded as soon as the subject signs the ICF and throughout the study. AEs should be reviewed and updated at each visit.

9.9.2 Safety Laboratory Evaluations

Subjects should fast for 8 hours prior to each visit that includes laboratory sampling.

The central laboratory will be responsible for providing preliminary and final laboratory reports to the sites and for sending “alert” values to both the Principal Investigator and Sponsor or a designee. The PI should review, comment, sign, and date the final laboratory reports. All out-of-range and “alert” laboratory values are to be evaluated by the PI for clinical significance and classified as:

- Abnormal, not clinically significant
- Abnormal clinically significant

Any clinically significant laboratory parameters observed at screening should be documented as medical history.

A new or worsening clinically significant laboratory value observed at any time after screening should be further assessed, monitored and documented as an AE on the AE eCRF.

9.9.3 Clinical Laboratory Tests

Clinical laboratory tests are detailed in Table 6. They will be performed according to the schedule of activities (See Section 8.2).

Reference ranges for all laboratory parameters are provided in the laboratory manual.

Table 6: Clinical Laboratory Tests

Category	Parameters
Serum biochemistry	Sodium, potassium, chloride, calcium, phosphorus, blood urea nitrogen (BUN), albumin, bilirubin (direct and total), ALT, AST, GGT, alkaline phosphatase, cholesterol (total cholesterol, LDL, apoB, non- HDL cholesterol and HDL cholesterol), triglycerides, hs-CRP
Hematology Complete blood count (CBC)	Hemoglobin, Hematocrit, Red Blood Cells count (RBC), MCV, White Blood Cells count + differential, Neutrophils, Basophils, Eosinophils, Lymphocytes, Monocytes, Platelet count
Serology	HBV, HCV (for subjects positive for hepatitis C antibodies, sustained virologic response (SVR) should be confirmed) and HIV
Renal function	Creatinine, eGFR
CPK	Creatine kinase
Thyroid function	TSH, T3 and T4
Urinalysis	pH, Blood, Glucose, Ketones, Erythrocytes, Protein, Specific Gravity (USG), Nitrite, Leukocytes, Bilirubin, Urobilinogen
Coagulation	Fibrinogen, prothrombin time/INR, aPTT
Glycemic Parameters	Fasting glucose, HbA1c, C-peptide, Insulin and HOMA-IR

Instructions for the preparation, handling, storage, and shipment of specimens will be detailed in the study's manual of procedure.

9.9.4 Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded at all study visits. The subject should rest in a recumbent position for at least 10 minutes before the ECG is taken.

The ECG will be evaluated by the Investigator at the time of performance (signed and dated) and the printout should be kept in the source documentation file. Additionally, until the Sponsor instructs otherwise, starting from the baseline visit all ECGs will also be sent to a central ECG laboratory. The centralized review will be done by a cardiology specialist who will provide an ECG report and notifications to the site. The report will provide an overall interpretation of the ECG, flagging clinically relevant ECG abnormalities based on a pre-defined set of abnormality criteria. Reports with pre-defined abnormalities will be sent to both the Principal Investigator and Sponsor or a designee.

If potentially clinically significant findings are detected by the Investigator or by the central reading, a local cardiologist should be consulted. All communications and diagnoses should be filed in the source documentation file.

Any ECG finding that is judged by the Investigator as a clinically significant change compared with baseline will be considered an AE, recorded and monitored.

The final decision whether the ECG findings are of clinical significance is the Investigator's responsibility.

9.9.5 Pregnancy Test

Pregnancy should be avoided during study and one month after discontinuing treatment. All females of childbearing potential must practice a highly effective method of contraception throughout the study period and for 1 month after treatment discontinuation. Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control.; see Section 6.1).

Any subject who becomes pregnant during the study period must not receive additional doses of study drug.

Pregnancy test (Serum β-hCG) will be performed for women of childbearing potential during the Screening visit. During the study, a urine pregnancy test will be performed at every study visit and according to local regulations.

A woman that suspects pregnancy should perform a pregnancy test, report results to the Investigator and in the event of positive results, discontinue treatment.

Results of the pregnancy test will be documented on the pregnancy eCRF page.

9.9.6 Vital Signs

Vital signs will be performed at all scheduled and unscheduled visits.

- Heart rate
- Blood pressure (Diastolic, Systolic)
- Temperature
- Respiratory rate

Blood pressure and pulse will be recorded in a sitting position after resting for 5 minutes.

For any abnormal vital sign finding, further assessment should be performed as deemed necessary by the Investigator.

9.9.7 Physical Examinations

Physical examinations will be performed at Screening, Baseline, week 24, 48, 72 and every 24 weeks thereafter as well as at early termination/study completion.

- General Appearance
- Head, Ears, Eyes, Nose, Throat
- Thyroid
- Cardiovascular
- Respiratory
- Gastrointestinal

- Skin
- Musculoskeletal
- Nervous System
- Lymph Nodes

Clinically significant changes from the initial physical findings at screening observed in subsequent visits will be considered AEs and will be documented on the AE eCRF.

9.9.8 Body Measurements

Body measurements will be measured at Screening, Baseline, week 12 and at every visit thereafter as well as at early termination/study completion.

- Body Weight
- Waist Circumference
- Height (measured only at Screening visit)

10 SAFETY AND PHARMACOVIGILANCE

Safety assessments will consist of evaluating relevant medical history, AEs and SAEs, laboratory parameters including chemistry, hematology and coagulation, vital signs, ECG, physical examinations, and documentation of all concomitant medications and/or therapies. The methods and timing of safety assessments are provided in Section ? and will be performed in accordance with the schedule in Table 3 and Table 4

The study will closely be monitored by an independent Data Monitoring Committee (DMC) according to a pre-defined DMC charter. The DMC will periodically meet (at least every 3-4 months) to assess the study progress and conduct, accumulated safety data, and as appropriate, pharmacokinetic and efficacy data.

The DMC can make recommendations regarding stopping or modifying the overall study. The DMC will convene on a regular basis and on an ad-hoc basis as outlined in the DMC charter.

The DMC will be composed of independent physicians with expertise in the liver field and other relevant experts. Members of the DMC cannot be investigators in the study. An external independent unblinded statistician will prepare the reports for review by the DMC.

During the study, pre-defined clinical outcome events, possible DILI events and major adverse cardiovascular events will be adjudicated by independent adjudication committees.

- **Clinical Outcome Adjudication Committee (COAC)** will adjudicate predefined clinical outcome events (all-cause mortality, liver transplant, progression to cirrhosis, change in MELD score to > 15 and hospitalization due to hepatic decompensation events)
- **Cardiac Adjudication Committee (CAC)** will adjudicate Major Adverse Cardiovascular Events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), hospitalization for unstable angina or heart failure, and all-cause mortality. Event

definitions will be based on the Standardized Definitions for Cardiovascular Endpoint Events in Clinical Trials[20,21].

- **Hepatic Safety Adjudication Committee (HSAC)** will adjudicate hepatic safety events including cases of suspected DILI as well as non-endpoint hepatic/hepatobiliary SAEs

The DMC will be provided the outcome of the adjudication.

10.1 Adverse Events

10.1.1 Definition of an Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The following medical events will be considered AEs:

- Any new medical condition, sign, symptom or disease or any worsening of pre-existing condition (in severity or frequency) following signing of ICF
- Worsening of a pre-existing disease should be recorded as an AE only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in this patient
- An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if any of the below are met:
    - Results in subject's temporary or permanent discontinuation of treatment or withdrawal by the Investigator
    - Is associated with clinical signs or symptoms
    - Is considered by the physician to be of clinical significance
- Any procedural complication

The following events will not be considered AEs:

- A chronic condition diagnosed during screening will be recorded as medical history and not as an AE
- Pre-existing disease, condition or laboratory abnormalities present before study entry (ICF signature) that does not worsen during the study
- Pre-planned elective hospital admission (planned prior to the study enrollment) for treatment or diagnostic procedure of a pre-existing condition, that has not significantly worsened
- A biopsy performed as part of the study is not considered an AE and hospitalization for liver biopsy, when required as standard of care for liver biopsy, and without complications is not considered an SAE

- Medical or surgical procedures are not considered AEs, rather, the condition leading to the procedure is the AE (e.g. anemia and not blood transfusion, appendicitis and not appendectomy)
- Abnormal laboratory values that in the Investigator's opinion are not clinically significant and do not require any intervention should not be reported as AEs

10.1.2 Recording and Reporting Adverse Events

AEs fall into the categories of "nonserious" and "serious". All AEs must be recorded on source documents and eCRF from the time the subject has signed the informed consent until the EoS or early termination (ESD) visit, regardless of apparent causality from use of the study drug.

At each visit, subjects should voluntarily report any AEs in response to general nonleading questions (e.g., "How have you been feeling since your last visit?"). For each AE reported by subjects, clinical site personnel should obtain all required information to complete the eCRF.

The AE term, date of onset, severity, seriousness, action taken, Investigator opinion of relationship to the study drug, outcome and date of resolution will be recorded in source documents and eCRF following the Investigator's assessment. If an ongoing AE worsens or improves in its severity, the maximum severity that occurred over the duration of the event should be recorded in eCRF.

AE verbatim terms provided by the Investigator will be coded using the current Medical Dictionary for Regulatory Activities (MeDRA) Version.

AEs classified as serious must be recorded on the appropriate SAE form and reported using the expeditious handling of SAE procedures to comply with regulatory requirements (see Section 10.1.5.3).

10.1.3 Severity of an Adverse Event

Severity of AEs should be assessed by the Investigator according to Common Terminology Criteria for Adverse Events (CTCAE) definitions as follows:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL; which refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (which refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4:** Life threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

A Semi-colon (;) indicates 'or' within the description of the grade.

Severity is not synonymous with seriousness. For example, a severe headache is not necessarily an SAE. However, mild chest pain may result in a day's hospitalization thus meeting serious criteria and would be considered an SAE.

10.1.4 Relationship of an Adverse Event to the Study Drug

The relationship of an AE to the study drug should be assessed by the Investigator using clinical evaluation and the following classification and considerations:

No reasonable possibility - not related: There is not a reasonable possibility that the administration of the study intervention caused the event or there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Reasonable possibility - related: The AE is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the AE or there is a temporal relationship between the study intervention and event.

Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

10.1.5 Serious Adverse Events

10.1.5.1 Definition of a Serious Adverse Event

Any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- An important medical event which requires medical intervention to prevent any of the above outcomes

The term "**life-threatening**" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

The term "**Inpatient hospitalization**" or prolongation of existing hospitalization means that the event required at least 24 hours hospitalization and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event.

The term "**Important medical event**" are those which may not be immediately life-threatening but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

10.1.5.2 Expectedness

The expectedness of an AE is defined in accordance with the Reference Safety Information. For a detailed description refer to the current IB.

An **unexpected** AE is an AE for which the nature or severity is **not consistent with the Reference Safety Information**.

10.1.5.3 SAE Reporting

The Sponsor is required to expedite to regulatory authorities reports of specific SAEs that occur during the study. SAEs must be reported to the Sponsor (or its designee) by the Investigator/site personnel as soon as they become aware of the event and no later than 24 hours regardless of relationship to the study drug.

SAE report form completion and reporting must not be delayed even when information is incomplete at the time of the initial report.

Any additional (follow-up) information that becomes available after the initial reporting, should be forwarded in a follow-up SAE report form by the site personnel within 24 hours of the information becoming available.

All SAEs should be reported to Sponsor or its designee following the completion guidelines provided with the study SAE form. All SAEs should be followed until resolution or stabilization and all parameters (including laboratory) return to baseline or until the Investigator assesses them as stable or until the patient is lost to follow-up. SAEs must be collected and reported during the study and up to 30 days after study completion. The Investigator does not need to actively monitor subjects for AEs once the study has ended, but SAEs occurring to a patient should be reported to the Sponsor, if the Investigator becomes aware of them. SAEs occurring any time after the reporting period must be promptly reported if a causal relationship to the study drug is suspected.

10.2 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities.

Sponsor or its designee is responsible for reporting all applicable SAEs to Regulatory authorities, Investigators, and IECs/IRBs, as applicable, in accordance with national regulations in the countries where the study is conducted.

Suspected Unexpected Serious Adverse Reactions (SUSARs) should be reported as expedited safety reports to all participating Investigators, ethics committees, and applicable regulatory authorities in accordance with ICH guidelines and the local regulatory requirements. The SUSARs will be submitted within 7 days for fatal and life-threatening events and within 15 days for other SUSARs events.

The Sponsor should submit all safety updates and periodic reports to the regulatory authorities, as required by applicable regulatory requirements.

Investigators should report to their local IEC/IRB as dictated by their board's policies and procedures.

The blinding will be maintained for the team who are involved directly in the study. For SUSAR reporting, dedicated personnel may break the subject's code without revealing the blind to the Sponsor personnel, its designee or site team.

10.3 Pregnancy Reports

A female clinical trial subject must be instructed to inform the Investigator immediately if she becomes pregnant during the study. Pregnancies occurring up to 30 days after treatment discontinuation must also be reported to the Investigator.

The Investigator should report all pregnancies to Sponsor or its designee within 24 hours of becoming aware of them, using a clinical trial pregnancy reporting form.

All pregnancy reports will be captured in the safety database.

If the subject requests to know which treatment she received, this information will be provided to her (see Section 8.4.4).

The pregnancy should be followed for outcome of the mother and the child, including any premature terminations, and all outcomes should be reported to Sponsor or its designee.

11 STATISTICAL METHODOLOGY

11.1 Open-Label Part

A total of 150 subjects, including those already randomized to Aramchol 300mg BID or placebo, will be randomized in a ratio of 1:1:1 to receive Aramchol 300mg BID according to the below grouping:

- Group A: The post-baseline liver biopsy will be conducted at week 24
- Group B: The post-baseline liver biopsy will be conducted at week 48
- Group C: The post-baseline liver biopsy will be conducted at week 72

Randomization in the Open-Label Part will employ a semi-minimization algorithm to balance the 3 groups in number of subjects, distribution of subjects according to fibrosis score (F1, F2 and F3), presence or absence of T2DM, and prior exposure to Aramchol 300mg BID. F1 subjects will be capped to enroll no more than 30 subjects.

[redacted]

[redacted]

11.2 Randomized, Double-Blind, Placebo-Controlled Part:

A total of 2000 subjects will be randomized into this study in a 2:1 ratio to treatment with Aramchol or with placebo, respectively.

[redacted]

[redacted]

11.2.1 Randomization

An eligible subject will randomly be allocated to treatment with Aramchol or matching placebo based on a randomization scheme employing a 2:1 assignment ratio, respectively, using permuted blocks stratified by country/geographical region (CGR) and by baseline Fibrosis stage (F2 or F3). [redacted]

[redacted]

11.2.2 Study Primary Endpoints

The primary efficacy endpoints for this study are:

- Histology-Based: The Histology-Based primary endpoint will be derived from the week-72 biopsy of the initial 1000 subjects as compared to baseline biopsy and will use:
  - ✓ **Resolution of NASH** defined as the Proportion (%) of subjects with resolution of NASH (defined by Ballooning of 0 and inflammation 0-1) and no worsening of liver fibrosis on NASH CRN fibrosis score (≥ 1 stage increase).

  OR
  - ✓ **Improvement in Fibrosis** defined as the Proportion (%) of subjects with improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation or steatosis)

- Clinically-Based: The Clinically-Based primary endpoint is the time to first occurrence of any of the following adjudicated events:
  - ✓ All-cause mortality
  - ✓ Liver transplant
  - ✓ Histological progression to cirrhosis
  - ✓ MELD score >15 if baseline MELD score was <12
  - ✓ Hospitalization due to hepatic decompensation event(s) including:
    - Hepatic encephalopathy grade ≥2 (as assessed by West Haven scale)
    - Variceal bleeding
    - New onset ascites requiring treatment
    - Spontaneous bacterial peritonitis as assessed by either positive cell culture or cell count

  Events will be adjudicated by an independent adjudication committee.

[redacted]

- ✓ [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
  - [redacted]
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[redacted]

[redacted]

[redacted]

11.2.7 Comparability of Study Groups at Baseline

Demographics and baseline data will be displayed for the ITT Analysis Set. Subjects' demographics and baseline characteristics, including baseline prognostic factors will descriptively be examined to assess the comparability of the treatment groups. For continuous variables, descriptive statistics (number [n], mean, standard deviation (SD), standard error, median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented.

Summary statistics of these parameters will also be provided when broken down by CGR, and by US/Non-US sub-populations.

11.2.8 Primary Estimands of Interest

11.2.8.1 Week-72 Histology-Based Primary Estimand

The primary Estimand for the Week-72 Histology-Based study part will be based on the effectiveness assumption (de-facto) using treatment policy. The primary Estimand construction elements of this Estimand are:

1. Population: Subjects with Nonalcoholic Steatohepatitis (NASH) that were randomized to the study.
2. Variables of interest: Week-72 (-2 Weeks, +6 Weeks) individual subject **Resolution of NASH,** OR, **Improvement in Fibrosis.**
3. Inter-current events: Subjects that ESD during the Histology-Based study part. The treatment-policy Estimand will be used to assess the benefit of Aramchol as compared to

placebo in initially randomized subjects' as actually observed regardless of the occurrence of ESD during the Histology-Based study part.

4. Population-level summary: The between groups difference in the proportion of subjects with **NASH Resolution** AND/OR the between groups difference in the proportion of subjects with **Improvement in Fibrosis**.

The treatment effect will be attributable to the subject's with NASH initially randomized to the study and who had the baseline and Week-72 liver biopsies regardless of ESD during the Histology-Based study part.

11.2.8.2 EoS Clinically-Based Primary Estimand

The primary Estimand for the EoS Clinically-Based study part will be based on the effectiveness assumption (de-facto) using treatment policy. The primary Estimand construction elements are:

1. Population: Subjects with Nonalcoholic Steatohepatitis (NASH) that were randomized to the study.
2. Variables of interest: Time to first occurrence of the adjudicated events.
3. Inter-current event: Subjects that were early discontinued from the study (ESD). The treatment-policy Estimand will be used to assess the benefit of Aramchol as compared to placebo in initially randomized subjects' as actually observed regardless of the occurrence of ESD.
4. Population-level summary: The difference in survival distributions/percentiles observed in the Aramchol arm as compared to the Placebo Arm.

The treatment effect will be attributable to the subject's with NASH initially randomized to the study regardless of study early discontinuation.

11.2.9 Efficacy Endpoints and Analyses

11.2.9.1 Primary Endpoints and Principal Analysis of the Study Primary Endpoints

The study identifies two primary endpoints: The Histology-Based endpoint and the Clinically-Based endpoint. The principal analysis sets for inference for these two primary endpoints will be the corresponding ITT Analysis Sets.

11.2.9.2 Principal Analysis of the Histology-Based Primary Endpoint

Within the work-frame of the Week-72 primary efficacy endpoint, the following two alternative outcome measures will be analyzed, separately, for assessing the efficacy of Aramchol as compared to placebo:

- Resolution of NASH
- Improvement in Fibrosis

The below described principal analysis will be conducted separately for **Resolution of NASH** and for **Improvement in Fibrosis.**

- The Histology-Based ITT Analysis Set (Histology-Based-ITT) will serve as the primary Analysis Set for efficacy assessment of the Histology-Based primary endpoint for the primary Estimand.
- Missing week 72 biopsy values will be handled concurrently by deterministic rules (e.g. subject who experience clinical events before week 72 will be considered treatment failures) and by multiple imputations procedures (MI).
- The analysis of the Histology-Based primary endpoint will be conducted using the imputed datasets and will employ the Cochran-Mantel-Haenszel (CMH) test (SAS® PROC FREQ) stratified by baseline Fibrosis stage (F2 or F3), baseline NAS score (<6 or ≥6), presence or absence of T2DM at baseline and country/geographical region (CGR).
- The Wilson-Hilferty transformation will be used to normalize the CMH test statistics and the Rubin's rule will be applied for combining the results to obtain the p-value.
- The magnitude of treatment effect estimate and its 95% CI will be calculated using the combined stratified difference in proportions using CMH weights.
- More details on imputation modeling and sensitivity analyses will be provided in the Statistical Analysis Plan (SAP).

11.2.9.3 Principal Analysis of the Clinically-Based Primary Endpoint

The Clinically-Based primary endpoint is the time to first occurrence of any of the following adjudicated events:

- All-cause mortality
- Liver transplant
- Histological progression to cirrhosis
- MELD score >15 if baseline MELD score was <12
- Hospitalization due to hepatic decompensation event(s) including:
  - ✓ Hepatic encephalopathy grade ≥2 (as assessed by West Haven scale)
  - ✓ Variceal bleeding
  - ✓ New onset ascites requiring treatment
  - ✓ Spontaneous bacterial peritonitis as assessed by either positive cell culture or cell count

[redacted]

[redacted]

11.2.10 Key Secondary Endpoint and Analysis

One key secondary endpoint, namely, **5-Year Proportion (%) of Subjects with Improvement in Fibrosis,** is defined for the EoS Clinically-Based study part. This endpoint will be tested for the primary Estimand using the Clinically-Based-ITT Analysis Set.

The statistical methodology for the analysis of this endpoint will follow the one described for the Biopsy-Based primary endpoint and will be provided in detail in the SAP.

[redacted]

[redacted]

11.3 Safety Analyses (both study parts; Open Label Part and Randomized, Double Blind, Placebo Controlled Part)

Safety analyses will be performed for the Safety Analysis Set (ST) and for the extended safety Analysis Set (eST).

11.3.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment. In this study, any AE occurring after the subject has signed the ICF should be recorded and reported as an AE.

The MedDRA dictionary will be used to standardize the terms used by the Investigator to describe the AEs.

The following will be incorporated into the analysis of adverse events:

- As analysis of AEs can incorporate only coded AEs, it is mandatory that at the time of database lock all AEs will be coded.
- Adverse events analyses will include only the Treatment Emergent Adverse Events (TEAEs), namely, those events which started on the day of randomization or afterwards. AEs lacking start day will be considered as TEAE.
- Analyses of TEAEs will include the display of cumulative incidence proportions (no. of subjects reporting at least one TEAE per category), exposure adjusted incidence rates of the number of TEAEs, and estimated differences and confidence intervals for all pairwise treatment arm comparisons.

The following analyses which are pre-planned for adverse events will include:

- Most frequent TEAEs (>5% of subjects in at least one study arm) by Preferred Term (PT).
- TEAEs broken down by System Organ Class (SOC) and by SOC and PT according to MedDRA dictionary.
- Serious TEAEs by MedDRA SOC and PT, data listing as well as summary table of SAEs broken down by study trimesters (90 days each).
- TEAEs broken down by severity.
- TEAEs broken down by relationship to study drug.
- TEAEs broken down by action taken.
- TEAEs broken down by event outcome.
- TEAEs will be provided broken down by study group and subgroups.
- Adverse Events dictionary used to code Investigator's verbatim terms will also be provided.
- Individual subject listings of TEAEs and non-TEAEs.

11.3.2 Laboratory Data

Laboratory testing will be performed by a central laboratory facility and/or affiliated laboratories which work under the central laboratory regulations using the same reference normal ranges.

Analyses of safety central laboratory data will be performed in the following manner:

- Analyses events as defined below will include the display of cumulative incidence proportions (no. of subjects reporting at least one event per category), exposure adjusted incidence rates of the number of events, and estimated differences and confidence intervals for all pairwise treatment arm comparisons:
  - ✓ Post-randomization Potential Clinical Significance (PCS) lab values will be provided.
  - ✓ Abnormal values at any time after randomization day, calculated for subjects with normal values at baseline will be provided. Analysis will include, per tested parameter, those subjects with normal baseline and at least one post-randomization day measurements.
  - ✓ The distribution of maximal values of central laboratory AST, ALT and total bilirubin at any time after randomization day in term of the upper normal range multiples will be provided for subjects with normal AST, ALT and total bilirubin at baseline.

- Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal or High. Shift analysis of the categorical change from baseline to each scheduled visit and to the last observed value will be provided.
- Box-Plots of measurements done, figures of mean values ±SEs of changes from baseline as well as descriptive statistics for all laboratory quantitative parameters and changes from baseline will be provided by scheduled visits and treatment groups.

11.3.3 Vital Signs

Vital signs will be analyzed in the following manner:

- Cumulative incidence proportions (no. of subjects reporting at least one event), exposure adjusted incidence rates of the number of events, and estimated differences and confidence intervals for all pairwise treatment arm comparisons of post-randomization Potential Clinical Significance (PCS) vital signs values will be provided.
- Box-Plots of measurements done, figures of mean values ±SEs as well as descriptive statistics for all parameters and changes from baseline will be provided by scheduled visits and treatment groups.

11.3.4 Electrocardiogram ECG

The study Site Investigator classified each ECG as either “normal”, “abnormal not clinically significant (NCS)”, or “abnormal clinically significant (CS)”.

Analyses of ECG evaluations will be performed in the following manner:

- Cumulative incidence proportions (no. of subjects reporting at least one event), exposure adjusted incidence rates of the number of events, and estimated differences and confidence intervals for all pairwise treatment arm comparisons of post-randomization Potential Clinical Significance (PCS) ECG values will be provided.
- Box-Plots of measurements done, figures of mean values ±SEs as well as descriptive statistics for all parameters and changes from baseline will be provided by scheduled visits and treatment groups.

11.4 Tolerability Assessments

Tolerability assessment will be based on the number and percent (%) of subjects who early discontinued treatment (ETD) and early discontinued study (ESD) by withdrawal reason will be presented. Time to withdrawal will also be presented by Kaplan-Meier curves.

[redacted]

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory, Ethical, and Study Oversight Considerations

12.1.1 Compliance Statement

This study will be conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Consolidated Guideline E6 (R2) and any applicable national and local laws and regulations (e.g., Title 21 Code of Federal Regulations 21CFR Part 11, 50, 54, 56, 312, and 314, the Health Insurance Portability and Accountability Act of 1996 and codified at 45 CFR Part 160 & 164, European Union [EU] Directive 20/EC or Regulation EU No. 536/2014, as applicable, 2005/28/EC and Regulation EU No. 2016/679) and any and all applicable laws pertaining to privacy, security, breach notification, or data protection, or similar laws, statutes, rules, or regulations, as the same may be amended from time to time, including without limitations, the General Data Protection Regulation (EU 2016/679) ("GDPR"); and the Health Information Portability and Accountability Act of 1996 as amended by the Health Information Technology for Economic and Clinical Health Act (Title XIII of the American Recovery and Reinvestment Act of 2009), and their implementing rules and regulations codified at 45 C.F.R. Parts 160 and 164. Health Insurance Portability and Accountability Act ("HIPAA") ("Data Protection Laws"). Any occurrence of noncompliance will be documented.

The Investigators are responsible for performing the study in accordance with this protocol and the applicable Data Protection Laws referenced above for collecting, recording, processing, transferring and reporting the data accurately, securely, and properly. Agreement of each Investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the Sponsor and other forms as required by national authorities.

Each Investigator is responsible for ensuring the privacy, health, and welfare of the subjects during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. Each Investigator and the applicable study staff must be familiar with the background to, and requirements of, the study and with the properties of the study drug(s) as described in the IB and other prescribing information.

Further, each Investigator shall ensure that all personal or sensitive data (as defined under Data Protection Laws), related to data subjects (i.e., subjects, employees, etc.) shall be collected, processed, stored and transferred in compliance with applicable Data Protection Laws, and as detailed herein, in the Clinical Trial Agreement, or as otherwise instructed by the Sponsor from time to time. Notwithstanding the above, the Investigator responsibility to comply with Data Protections Laws is independent, regardless to instruction provided or not by the Sponsor.

The Principal Investigator has the overall responsibility for the conduct and administration of the study and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with local authorities.

12.1.2 Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

The protocol, IB, ICFs, any information which should be given to the subject and any additional relevant supporting materials required by ICH GCP guidelines, Data Protection Laws and the applicable regulatory authorities, must be submitted to the Independent Ethics Committee/ Institutional Review Board (IEC/IRB) for review and approval before the study is initiated.

No subject should be enrolled to the study before the IEC/IRB issues its written approval/ favorable opinion.

In case the Sponsor will amend the protocol, the protocol amendment must be submitted and approved by the applicable regulatory authority and relevant IEC/IRB prior to implementation except when necessary to eliminate immediate safety concerns to the subjects or when the change(s) involves only logistical or administrative aspects of the trial

The Investigator must follow the international and local requirements for IEC/IRB submission e.g. periodic status reports, SAEs, notification of study completion and study final report. When required, an extension or renewal of the IEC/IRB approval must be obtained and forwarded to Sponsor or designee.

The IECs/IRBs must supply the Sponsor with a list of the IEC/IRB membership and a statement to confirm that the IEC/IRB operates in accordance with the ICH GCP guidelines and the applicable laws, and regulations

12.1.3 Informed Consent Process

12.1.3.1 Consent/Assent and Other Informational Documents Provided to Participants

The informed consent process must be in accordance with the applicable regulatory requirements and must adhere to GCP ICH guidelines, 21 CFR Part 50 FDA regulations and ethical principles in the Declaration of Helsinki, as well as Data Protection Laws.

Prior to study initiation in an investigational center, the PI must have the IECs/IRBs written approval or favorable opinion of the written Informed Consent Forms (main ICF and Genetic ICF) and any other written information to be provided to subjects.

The written approval of the IEC/IRB, together with the approved subjects' information and ICFs, must be filed in the study files.

12.1.3.2 Consent Procedures and Documentation and Subject's Rights with Regards to Its Data

Freely given, specific, informed and affirmative consent should be obtained from every subject prior to any study-specific procedure takes place.

The Investigator, or a person designated by the Investigator, should fully inform the

subject or the subject's legally acceptable representative, of all pertinent aspects of the study including but not limited to the nature of the study, its purpose, the procedures involved, the

expected duration, the potential risks and benefits involved and any discomfort it may entail. The subject will also be informed about the importance of remaining in the study even if study medication is discontinued.

The subject must be further informed that its data, including personal data and health data, will be used in accordance with the Data Protection Laws, including with regards to its rights withdraw consent or request deletion of personal or sensitive data. Specifically, the subjects shall be clearly informed of the limitations set forth on deletion rights, and if applicable, limitations on withdraw consent.

The Investigator will communicate with Sponsor on behalf of the subject, however, the procedure followed upon such data subject request will be handled to Data Protection Laws and the Sponsor's instructions and guidance.

The Investigator or its designee, should provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject or the subject's legally acceptable representative. The informed consent process should be documented in the source documents.

Copies of the fully signed and personally dated Informed Consent Forms (ICF) and any other relevant written information will be given to the subject and the original ICFs will be properly maintained at site.

The written ICF and any applicable written information will be revised whenever important new information, relevant to the subject's willingness to continue participation, becomes available. This includes regulatory accelerated/conditional approval of Aramchol in the subjects' specific country. ICFs templates shall either be drafted by approved in writing by the Sponsor. Any revised written ICF, and written information will be submitted and approved by the IEC/IRB before using. The subject or the subject's legally acceptable representative should be updated in a timely manner and will be asked to review and consent to the revised approved ICF.

12.2 Confidentiality

All information supplied by Sponsor, or designee on its behalf, in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigators' Brochure, clinical protocol, case report forms, Subject's Data and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of the Sponsor, shall not be disclosed to others without the written consent of Sponsor, and shall not be used by the receiving party except for the performance of this study.

The information developed during the conduct of this clinical study is also considered Sponsor confidential information and will be used by Sponsor in connection with the development of the drug. In order to enable Sponsor the use of the information derived from this clinical

study, the Investigator is obliged to provide all protocol-specified data generated in this study to Sponsor.

The Sponsor is the sole owner of the original case report forms completed as part of the study.

By signing the clinical study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The information obtained during this study may be made available to other Investigators who are conducting similar studies.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol upon prior written consent from the Sponsor.

12.2.1 Subject Confidentiality

The Investigator must assure that the subjects' privacy and Subject's Data confidentiality and security will be strictly maintained. Subjects' Data will be identified by the assigned subjects' number and in accordance with local regulations.

The subject's personal data (such as name, address, contact details, identification number, etc.) shall not be shared or disclosed, directly or indirectly, with third parties, including the Sponsor, unless the Sponsor or its designee are physically at the site, or unless required under applicable law. In the event that personal data is disclosed, the Investigator shall promptly notify the Sponsor. Both the Sponsor and the Investigator shall handle such disclosure according to applicable laws, including Data Protection Laws.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. This list will be securely stored and will serve for internal use only. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

12.3 Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of study participants are protected, that the reported study data is accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), with applicable regulatory requirements and relevant Sponsor's Standard Operating Procedures.

The study monitor is the primary liaison between the Sponsor and the Investigator. The main responsibilities of the study monitor are to ensure adherence to the protocol, to ensure that informed consent is obtained and recorded for all subjects before they participate in the study and to verify that all study data are correctly and completely recorded and reported.

The study monitor will contact the Investigator and visit the investigational center at regular intervals throughout the study as defined by the study-specific monitoring plan. The study monitor will be permitted to check and verify the various records (eCRFs and other pertinent source data records) relating to the study, to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. The monitoring type, frequency, data verification extent and other monitoring activities will be defined in the specific study monitoring plan.

The PI or a designee must make available all source documents and regulatory documentation to Sponsor or designee and all applicable regulatory authorities. In accordance with ICH E6, source documents include but are not limited to the following: medical records; clinic, office, or hospital charts, recorded data from automated instruments such as ECGs, x-rays, and other imaging reports, laboratory reports, records of telephone contacts, drug inventory records.

Sufficient time must be allowed by the site personnel for the monitor to review study documents. The PI or a designee and other relevant personnel should be available to answer questions or resolve queries and to provide any missing information. The study monitor will adhere to the requirements for subjects' confidentiality and data security in a manner at least as strict as required herein.

12.3.1 Protocol Deviations

Protocol deviation is any noncompliance with the clinical study protocol, ICH GCP guidelines and the applicable regulatory requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. If noncompliance occurs, corrective actions should be developed and implemented promptly by site staff.

Each protocol deviation should be recorded and managed according to the monitoring plan. The protocol deviations will be reported to the applicable IEC/IRB as required.

This study will be conducted as specified in this protocol except for situations where immediate intervention is required to eliminate safety risk based on the Investigator or professional designee judgment.

12.4 Quality Assurance and Quality Control

The Sponsor and designee will implement and maintain quality assurance and quality control systems to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines, including ICH GCP guidelines and Data Protection Laws. Data management and control processes specific to this study, along with all steps and actions taken regarding Data Management and data quality assurance, will be described in a data-management plan.

Case report forms received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding

conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be reconciled with the information available in the CDMS (clinical data management system). Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

All recorded data will be entered into a password protected database. All data entry forms will be accessed and completed electronically through a password-protected log-on. All user interaction with the web-based system, from transmitting access passwords to entering sensitive Subject Data, is done using the secure HTTPS protocol. Firewalls will be implemented to ensure that only the minimum traffic required for normal operations is allowed to traverse the network of web and database servers. The database production servers will be housed in secure institutional data center facilities and include failover protection designed to minimize potential for server downtime. Minimal required personnel are allowed direct access to production facilities. The study data will remain secure and be maximally protected using production level data center servers, all, in accordance and without derogating from the requirements under Data Protection Laws

12.5 Audits and Inspections

The Sponsor or designee, regulatory authorities and IECs/IRBs may perform audits or inspections to the investigational centers to evaluate study conduct and compliance with protocol, SOPs, ICH GCP guidelines, and applicable regulatory requirements. Participants' confidentiality and privacy will be strictly held in trust by all parties.

The Sponsor and/or designee will establish an audit plan and procedures for study audits.

The Investigator should grant direct access to source data/documents, medical records (following subjects' signature on ICF), facilities and any other resources that are deemed to be related to the clinical study for monitoring, auditing, IEC/IRB review, and applicable regulatory authority inspection.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

12.6 Data Handling and Record Keeping

12.6.1 Data Handling and Source Data Recorded on the Case Report Form

Data will be collected and stored using electronic CRFs that are specifically designed for this study and in accordance with applicable law requirements.

Subject's personal data and records are strictly confidential and will be collected, handled, processed and stored in a secure manner and in full compliance with applicable Data Protection Laws.

The data collected on the CRFs will be stored in a Clinical Data Management System (CDMS) that meets the technical scientific, regulatory, and logistical requirements of the study, including without limitations the technical requirements described in 21 CFR part 11 as well as applicable Data Protection Laws, prior to storing the study data.

Access to the CDMS will be provided following training on the system and any study-specific training. Solely users with the need to know will be provided with individual system access rights, after they commit themselves to confidentiality or appropriate statutory obligation of confidentiality including with regards to the confidentiality of Subject's Data, their access permissions, and permitted use of Subject's Data.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each subject who provided ICF in accordance with applicable laws. Subject identity, including any identifying data, should not be discernible from the data provided on the CRF. Data will be verified using the source data by the study monitor and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved in the system by the Investigator at the investigational center. This approval acknowledges the Investigator's review and acceptance of the data as being complete and accurate.

All subject data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the CRF. Data may not be recorded directly onto the CRF and considered as source data unless the investigational center obtains written documentation from the Sponsor, before the beginning of the study, indicating which data are permitted to be recorded directly onto the CRF.

If data are processed from other than subject clinical sources (e.g. central laboratory, bioanalytical laboratory, central reading center), the results will be sent to the study site, in a secure and encrypted manner, where they will be retained and might be transcribed to the CRF, if applicable. These data sets may also be sent electronically to the Sponsor (and/or organization performing Data Management) as part of the clinical database. All data from other sources will be available to the Investigator(s).

For subjects who sign the ICF and perform screening procedures but do not enroll in the study, for any reason, the required data will be entered into the CRF, according to the instructions detailed in the eCRF completion guidelines.

Any processing of Subject's Data shall be solely to the extent required and subject to the informed consent provided, for the purpose of complying with data minimization principles. No additional data shall be processed without applicable informed consent. Further, Subject Data shall be used or shared solely for the purpose of the study, as set forth herein or otherwise instructed by the Sponsor in writing and consented by the subject. Using Subject's Data for any other purposes is strictly forbidden.

12.6.2 Study Discontinuation and Closure

All 2000 subjects planned to be randomized into the Randomized Double-Blind, Placebo-Controlled Part will receive Aramchol or matching placebo until EoS which will be announced at the time when a total of 380 subjects will experience at least 1 pre-specified clinical event or at 5 years from last subject randomization, whichever comes first.

The Open-Label Part will continue for the same duration as the Randomized, Double-Blind, Placebo-Controlled Part.
All subjects in the Open-Label Part will receive Aramchol 300mg BID until End of study (EoS).
Premature termination or suspension of this study may occur due to regulatory authority decision, IEC/IRB opinion, drug safety reasons, and DMC recommendation or at the discretion of the Sponsor. The Sponsor retains the rights to discontinue the development of the investigational product at any time.

If the study is prematurely terminated, the Sponsor will promptly notify the Investigators and the relevant regulatory authorities as required. The Investigator should promptly notify the IEC/IRB and the study participants and assure appropriate therapy and follow-up.

12.6.2.1 Declaration of the End of the Clinical Trial

For clinical investigational centers, EoS declarations will be in accordance with local regulations.

12.6.3 Study Records Retention

The Investigator or institution shall retain all essential study documentation and records generated before, during, and after the study ("Study Records"). The Study Records should be kept at the clinical site or a designated, secured, off-site storage facility with limited access.

The Sponsor specific essential documents and The Study Records should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

If the Investigator becomes unable to continue to retain Study Records for the required period, the Sponsor should be prospectively notified, and the study records must be transferred to a designee as agreed by the Sponsor.

12.7 Future Use of Stored Specimens and Data

The Study Records, aggregated data and statistics as well as certain study subjects' personal information and biospecimens (such as blood samples or tissue biopsies) collected during the study may be stored and used for future research. Personal information and samples from this study that will be used for future research may be coded (include the study subject code) or de-identified. If any future research requires use of de-identified or anonymized personal information or samples, all personal identifiers will be removed from them, including the study code, so that the information or samples will be considered to be de-identified or anonymized as defined under applicable Data Protection Laws and cannot be linked back to the subject.

If required by law, the Investigator shall ensure the subject consents to future use of their samples and information through the ICF

The aforesaid coded, de-identified or anonymized samples and information may also be shared with third parties with whom the Sponsor collaborates even if it exceeds the scope of the clinical trial.

12.8 Reporting and Publication of Results

The Sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements for registration in clinical trial registries and posting of results. This study will be registered on clinical trials registry websites according to standard procedures.

The Sponsor is responsible for preparing a clinical study report, in cooperation with the Principal Investigator.

No data that result from the study and none any of the information provided by the Sponsor to the Investigators for the purpose of conducting the study, will be published or passed on to any third party, without prior written consent of the Sponsor. Policies regarding the publication of the study results are defined in the Clinical Trial Agreement.

No patent application(s) based on the results of the study may be made by the Investigator or Institution nor may assistance be given to any third party to make such an application without the written authorization of the Sponsor.

12.9 Liability and Insurance

This clinical study is insured in accordance with the corresponding local legal provisions.

The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions.

Excluded from the insurance cover are, inter alia, damages to health and worsening of previous existing disease that would have occurred or continued if the subject had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the Sponsor where required.

12.10 Vendors

Certain study activities will be performed by Sponsor-designated vendors. These may include, among others, a contract research organization, a central laboratory, biopsy reading center, clinical supply management, and data management. The list of vendors is available in the trial master file and will be updated as necessary.

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