Study Protocol	
Official title:	A Phase II, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of CS0159 in the Treatment of Patients with Nonalcoholic Steatohepatitis (NASH)
NCT Number:	NCT05591079
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TITLE PAGE

Protocol

A Phase II, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of CS0159 in the Treatment of Patients with Nonalcoholic Steatohepatitis (NASH)

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Sponsor:
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SYNOPSIS

Title of study: A Phase II, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of CS0159 in the Treatment of Patients with Nonalcoholic Steatohepatitis (NASH)
Indication: NASH
Number of Investigators and study centers: Up to 25
Development phase: II
Objectives: The primary objectives of the study are: Safety • To evaluate the safety and tolerability of CS0159 in patients with NASH treated over 12 weeks. Efficacy • To assess the changes in liver steatosis through magnetic resonance imaging (MRI) proton density fat fraction (PDFF) from baseline to Week 12. The secondary objectives of the study are: Pharmacokinetics (PK) and pharmacodynamics (PD) • To assess the PK and PD profiles of CS0159. Efficacy • To assess the inflammation changes in alanine aminotransferase (ALT) levels from baseline to Week 12. The exploratory objectives of the study are: • To explore the changes in liver steatosis, inflammation, and fibrosis through a set of target biomarkers from baseline to Week 12. • To explore changes in inflammation through iron-corrected T1 (cT1) from baseline to Week 12. • To explore the dose-response relationship of CS0159 on markers of hepatic steatosis, inflammation, and fibrosis in NASH from baseline to Week 12. • To explore the dose-response relationship of CS0159 on metabolic markers.

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Methodology/study design:

This will be a multicenter, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, PKs, and efficacy of CS0159 in the treatment of patients with NASH over 12 weeks.

Potential patients will be screened from Day -56 to Day -1 to assess their eligibility to enter the study. Imaging biomarkers noninvasive testing will be performed through MRI-PDFF and cT1 mapping, but no liver biopsy.

Additionally, patients enrolled at a site with the capability to conduct magnetic resonance elastography [MRE]) will have the option to undergo the MRE testing at the screening period and at Week 12 of this study.

Patients will be randomized in a 2:2:1 ratio using an interactive web response system (IWRS) to receive matching CS0159 1.4 mg, 2 mg, or placebo tablets once daily, respectively. Randomization will be stratified by diabetes status.

On Day 1, the following assessments will be performed predose: physical examination, urine pregnancy test, vital signs, wet biomarkers, PK/PD assessments, and pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale). In addition, clinical laboratory will be performed on Day 1.

There will be a total of up to 8 visits to the clinical site and 1 phone call visit on Week 9, including up to 2 screening visits; IWRS randomization on Day 1; and visits on Day 7 (Week 1), Day 21 (Week 3), Day 42 (Week 6), Day 63 (phone call at Week 9), and Day 84 (Week 12). A final safety follow-up visit will occur on Day 112 (Week 16).

Number of patients:

It is anticipated that approximately 100 patients will be enrolled and randomized into the study in a 2:2:1 ratio (40:40:20 patients per arm).

Diagnosis and main criteria for inclusion and exclusion:

The following are the main inclusion criteria:

1. Patients capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.
2. Male and female patients of any ethnic origin aged 18 to 75 (inclusive) at the time of the ICF signature.

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3. Patients who meet at least 1 of the following criteria for the diagnosis of NASH:
   a) Biopsy-proven NASH within 12 months of screening, defined by the NASH Clinical Research Network (NASH CRN) Histologic Scoring System: NAFLD activity score (NAS) ≥4 (with ≥1 point in each component of steatosis, lobular inflammation, and hepatocellular ballooning) AND stage 1, 2, or 3 fibrosis.
   b) Evidence of liver fat distribution ≥8% via MRI-PDFF within 3 months of screening.

4. Evidence of metabolic syndrome defined by the presence of at least 3 of the below criteria, except for those patients with biopsy-proven NASH:
   a) Waist circumference over 40 inches (men) or 35 inches (women).
   b) Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or on drug treatment for hypertension is an alternate indicator.
   c) Fasting triglyceride level ≥150 mg/dl or on stable and permitted drug treatment for elevated triglyceride.
   d) Fasting high-density lipoprotein cholesterol (HDL-C) level <40 mg/dl (males) or <50 mg/dl (females) or on drug treatment for reduced HLD-C.
   e) Fasting glucose levels ≥100 mg/dl or on stable and permitted drug treatment for elevated glucose.

5. Body mass index (BMI) >25 kg/m^2, NOTE: for Asian-Americans BMI >23 kg/m^2.
6. Stable use of other antidiabetic, weight loss, or lipid-modifying medications for at least 12 weeks prior to randomization.
7. Patients who agree to abstain from heterosexual activity, use adequate hormonal contraception, or use highly effective double barrier contraception (ie, a combination of condom or diaphragm AND hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system or documented vasectomy) during the study and for 12 weeks after the last dose of the study intervention, unless:
   a) Patient is a female of nonchildbearing potential, defined as a woman who had surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) at least 3 months before screening OR postmenopausal woman ≥45 years of age with >1 year since last menstrual period.
   b) Patient is a surgically sterilized male through vasectomy or bilateral orchiectomy at least 3 months before screening.
8. For women of childbearing potential, a negative serum pregnancy test at screening is to be conducted and must have a urine pregnancy test within 24 hours before the first dose of the investigational product (IP).
9. Male patients with female partners of childbearing potential should agree to use highly effective contraceptive measures from the screening visit through 12 weeks after the last dose of study drug. Highly effective contraceptive measures include documented vasectomy, abstaining from sexual intercourse,

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and double-barrier method (please see exclusion criterion 7). As there may be a risk of IP being secreted in the ejaculate, male patients (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and 12 weeks after the last dose of study drug. Male patients with female partners that are confirmed as postmenopausal are not required to use contraceptive measures.

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The following are the main exclusion criteria:

1. History of hypersensitivity to the IP or its excipients or drugs of similar chemical classes.
2. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
3. Previous exposure to farnesoid X receptor (FXR) agonists 3 months prior to the first dosing.
4. Current or within 6 months of screening use of drugs associated with steatosis, including but not limited to eg, methotrexate, amiodarone, high-dose estrogen, tamoxifen, long term systemic steroids, anabolic steroids, valproic acid.
5. Prothrombin time international normalized ratio >1.3, unless due to therapeutic anticoagulation.
6. Total bilirubin >upper limit of normal (ULN; except for patients with Gilbert's syndrome with a normal direct bilirubin value and normal reticulocyte count).
7. Platelet count <140 000/mm^3, absolute neutrophil count <1500 cells/mm^3, or total white blood cells <3000 cells/mm^3.
8. Alanine aminotransferase and aspartate aminotransferase (AST) >5 × ULN, or alkaline phosphatase (ALP) >1.5 × ULN.
9. Weight changes >10% in 6 months prior to screening, or weight changes >5% from the screening MRI-PDFF to randomization or from the time of the diagnostic liver biopsy to randomization, whichever is longer.
10. Poorly controlled hypertension (systolic >160 mm Hg, or diastolic blood pressure >100 mm Hg – mean of 3 measurements).
11. Uncontrolled diabetes mellitus (hemoglobin A1c >10.0% during screening).
12. Cirrhosis of the liver as defined by any of the following:
    a) Cirrhosis on historical liver biopsy (eg, Brunt/Kleiner Stage 4 or equivalent).
    b) Evidence of cirrhosis on liver imaging (eg, ultrasound, computed tomography, or MRE) including a nodular liver surface, splenomegaly, or portal venous collaterals.
    c) History of decompensated liver disease (ascites, hepatic encephalopathy, variceal bleeding).
13. Any of the following:
    a) History of or positive for human immunodeficiency virus (HIV) at screening.
    b) Chronic hepatitis B virus infection (hepatitis B surface antigen positive). For patients who are negative for HBsAg but are positive for either surface antibodies and/or core antibodies, HBV DNA polymerase

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chain reaction will be performed and if any test result meets or exceeds detection sensitivity, the patient will be excluded.

c) Chronic hepatitis C virus (HCV) infection (HCV antibody (HCVAb) and HCV ribonucleic acid [RNA] quantification positive). If the patient is HCVAb positive, then HCV RNA quantification by reverse transcription polymerase chain reaction (RT-PCR) will be performed. If the HCV RNA quantification is positive, then the patient will be excluded. Patients cured of HCV infection less than 2 years prior (based on the date of RNA PCR negative confirmation following the conclusion of treatment) to the screening visit are not eligible.

14. History of acute liver complications due to gallstones (eg, acute cholecystitis or acute biliary obstruction) unless the patient has had a cholecystectomy (more than 3 months prior to screening).
15. History of liver transplantation or causes of liver disease other than NASH, such as alcoholic liver disease, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, Wilson disease, iron overload, alpha-1-antitrypsin deficiency, drug-induced liver injury, known or suspected hepatocellular carcinoma.
16. Patients with contraindications to MRI imaging including:
    a) Brain aneurysm clip.
    b) Implanted neural stimulator.
    c) Implanted cardiac pacemaker or defibrillator, or presence of intracardiac wires.
    d) Prosthetic heart valves.
    e) Cochlear implant.
    f) Ocular foreign bodies that might be ferromagnetic (eg, metal shavings).
    g) Other implanted medical devices (eg, insulin pumps).
    h) Metal shrapnel or bullets still in the body.
    i) Severe claustrophobia.
    j) Tattoos (as determined by the investigator and imager).
    k) Weight in excess of MRI machine capacity.
17. Pregnant or nursing (lactating) women.
18. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the Alcohol Use Disorders Identification Test questionnaire ≥8.
19. Inability to reliably quantify alcohol consumption based on local study team's judgment.
20. History or evidence of ongoing drug abuse, within the last 6 months prior to randomization. Marijuana or cannabidiol use is not allowed if it is determined to be medically inappropriate by the investigator.

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21. History or presence of any disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the large intestine, eg, inflammatory bowel disease, prior or planned (during the study period) bariatric surgery (such as gastroplasty, roux-en-Y gastric bypass).
22. Body mass index >50 kg/m^2.
23. Estimated glomerular filtration rate ≤60 ml/minute/1.73m2 (calculated by the modification of diet in renal disease equation for the estimated glomerular filtration rate (MDRD)).
24. History or presence of chronic pruritus that is defined as pruritus lasting 6 weeks or more prior to the enrollment of the study.
25. Clinically significant ECG abnormalities or the corrected QT interval by Fridericia greater than 450 ms for males and 470 ms for females at either screening or baseline, or any prior history of QT abnormality.
26. Concomitant use of medications, food, and drinks that are strong or moderate cytochrome P450 (CYP)3A4 inhibitors or inducers within 14 days prior to the first dose of study drug and throughout the study duration.
27. Concomitant medications: vitamin E ≥800 IU/day, thiazolidinediones, glucagon-like peptide-1 agonists (GLP1a)(unless the subjects on a stable dose of GLP1a for diabetes mellitus ≥ 6 months before screening), sodium-glucose transport protein 2 inhibitors, and unstable dose (dose changes >30% in the last 30 days prior to screening) of insulin.
28. Any other condition(s) (including cardiovascular diseases) that would compromise the safety of the patient or compromise the quality of the clinical study, as judged by the investigator.
29. Initiated a structured weight loss or dietary program (Weight Watchers, Jenny Craig, physician prescribed program) within 3 months prior to randomization.
30. Initiated treatment with medications for weight loss within 6 months prior to randomization.
31. Patients with a history or diagnosis of:
    a) Solid organ transplantation and hematopoietic transplantation
    b) Multiple endocrine neoplasia (MEN I or MEN II)

Investigational products, dose, and mode of administration:

Investigational product: CS0159 (Linafexor) tablet.

Proposed dose levels: 1.4 mg daily and 2 mg daily.

Administration route: Oral.

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Reference therapy, dose, dose form, and mode of administration:

Reference product: Placebo.

Administration route: Oral.

Duration of patient participation in study:

Planned screening duration: up to 8 weeks.

Planned treatment duration: 12 weeks.

Planned safety follow-up visit: 4 weeks.

Planned total study duration (screening to follow-up): up to 24 weeks.

Study populations:

This study will include the following study populations:

- Safety Analysis Set (SAS): All randomized patients who receive at least 1 dose of the study drug or placebo. Patients will be analyzed according to the treatment received. The SAS will be the study population used for presentation of safety information.
- Full Analysis Set (FAS): All randomized patients who had at least one dose of study treatment. Patients will be analyzed according to their randomized treatment. The FAS will be the study population used for the presentation of efficacy analyses.
- PK Analysis Set: All randomized patients who receive an active study drug and who have any measurable plasma concentration of CS0159 for analysis. Patients will be analyzed according to the treatment actually received. The PK Analysis Set will be the study population used for presentation of PK information.

The primary safety endpoints of the study are:

- Incidence and severity of adverse events (AEs)/treatment-emergent AEs.
- Incidence and severity of adverse drug reactions.
- Clinical laboratory assessments (hematology, biochemistry, urinalysis, and hematopoietic and coagulation markers).

The primary efficacy endpoint is:

- The liver fat content (LFC) as measured by MRI-PDFF mean changes from baseline to Week 12.

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The secondary PK/PD endpoints of the study are:

Pharmacokinetics:

- Pharmacokinetic parameters of unchanged CS0159, including but not limited to the area under the curve ($AUC_{0-\infty}$, AUC_{0-last}, $AUC_{0-\tau}$), maximum concentration (C_{max}), time to maximum plasma concentration (t_{max}), half-life ($t_{1/2}$), and accumulation ratio of area under the concentration-time curve (AUC) in plasma.

Pharmacodynamics:

- Plasma concentrations and PD parameters of the biomarkers of FXR target engagement fibroblast growth factor 19 and serum 7α-hydroxy-4-cholesten-3-one (C4) from baseline to Week 12.

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The secondary efficacy endpoints of the study are:

- The proportion of patients with ≥30% reduction in liver fat through MRI-PDFF from baseline to Week 12.
- The ALT mean changes from the baseline to Week 12.
- The proportion of patients having a ≥30% reduction in ALT levels from the baseline to Week 12.

The exploratory endpoints of the study are the mean changes from baseline to Week 12 in:

- Inflammatory and fibrosis biomarkers (ALP, AST, gamma-glutamyl transferase, platelet count, cytokeratin-18), procollagen C3, and enhanced liver fibrosis (namely tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid).
- The proportion of patients with cT1 ≥880 ms at the baseline having a ≥80 ms (milliseconds) reduction in cT1 levels.
- Metabolic biomarkers (fasting glucose, insulin, homeostatic model assessment for insulin resistance index, hemoglobin A1c, and bile acids).
- Standard lipid panel (total cholesterol, calculated low-density lipoprotein cholesterol, HDL-C, and triglycerides).
- Lipid profile (nuclear receptor and metabolism-altering mechanisms of action).
- Insulin sensitivity index (lipoprotein insulin resistance index based on 6 lipoprotein parameters).
- Lipoprotein particle concentration and size including LDL-P, and HDL-P.
- GlycA and branched-chain amino acid concentrations.
- Bile acids profile (total), and C4 (an intermediate in the synthesis of bile acids from cholesterol and a biomarker of hepatic 7α-hydroxylase [CYP7A1] activity).

<u>Potential posthoc analysis:</u>

- NIS-4 (NASHnext). Serum will be saved for potential posthoc analysis of NIS-4 changes from baseline to Week 12 after the last dose of study intervention.

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Statistical methods:

Safety:

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

Efficacy:

The sample size of 40 patients per active dose group with 20 patients in the placebo group would provide 80% statistical power under the following assumptions:

- $\alpha = 0.05$, 2-sided test.
- Placebo mean % Δ from baseline in LFC = -10%, active mean % Δ from baseline in LFC = -25%.
- Common standard deviation= 19%.

Data Monitoring Committee Meetings:

Safety data in addition to PK and PD data will undergo formal review by an independent data monitoring committee that will meet at least once and ad hoc as needed and will be responsible for the oversight of the overall safety of the study.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
α-SMA	α-Smooth Muscle Actin
AE	adverse event
ADL	activities of daily living
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASBT	apical sodium-dependent bile acid transporter
AST	aspartate aminotransferase
AUC	under the concentration-time curve
AUDIT	alcohol use disorders identification test
BSEP	bile salt export pump
BMI	body mass index
BLM	baseline measurement
BUN	blood urea nitrogen
C4	7α-hydroxy-4-cholesten-3-one
cT1	iron-corrected T1
CFR	Code of Federal Regulations
CK-18	cytokeratin-18
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSA	clinical study agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
DMC	data monitoring committee
EC	ethics committee
EC_{50}	median effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
EOT	end of treatment
FAS	Full Analysis Set
FGF15	fibroblast growth factor 15
FGF19	fibroblast growth factor 19
FXR	farnesoid X receptor
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C virus antigen
HDL-C	high-density lipoprotein cholesterol
HFD	high fat diet
HIV	human immunodeficiency virus

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Abbreviation	Definition
HOMA	Homeostatic Model Assessment for Insulin Resistance
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IP	investigational product
IRB	institutional review board
IWRS	interactive web response system
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LFC	liver fat content
MAD	multiple-ascending dose
MEN	multiple endocrine neoplasia
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NIT	noninvasive test(ing)
NOAEL	no-observed-adverse-effect level
PBC	primary biliary cholangitis
PD	pharmacodynamics
PDFF	proton density fat fraction
PK	pharmacokinetic
PSC	primary sclerosing cholangitis
PSS	Patient Safety Solutions
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTcF	corrected QT interval by Fridericia
RNA	ribonucleic acid
SAD	single-ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCD1	Stearoyl-coenzyme A Desaturase 1
SHP	small heterodimer partner
SOC	system organ class (Medical Dictionary for Regulatory Activities classification)
STZ	streptozotocin
$t_{1/2}$	half-life
TBL	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglyceride
t_{max}	time to maximum plasma concentration
TNF-α	tumor necrosis factor α
ULN	upper limit of normal

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1. INTRODUCTION

Farnesoid X Receptor (FXR) belongs to the nuclear receptor family and has been shown to be an attractive research focus for cholestatic liver diseases like primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), in addition to being nonalcoholic fatty liver disease/ nonalcoholic steatohepatitis (NAFLD/NASH) clinical targets now. The multifaceted effects of FXR activation are involved in suppressing bile acids synthesis through 7α-hydroxylase (cytochrome P450 [CYP]7A1) downregulated by the induction of the ileal hormone fibroblast growth factor 19 (FGF19) and hepatic small heterodimer partner (SHP), reduction of basolateral bile acids uptake and increase of bile acids efflux, lowering lipid levels in the circulation through suppressing de novo fatty acid synthesis, increasing triglyceride (TG) hydrolysis, clearance, and fatty acid oxidation, as well as inhibiting neutrophil accumulation and proinflammatory cytokine signaling while avoiding complicated NF-κB signaling the cascades (Armstrong & Guo, 2017; Beuers et al., 2015; Stofan & Guo, 2020).

CS0159 is an FXR agonist drug aiming for the treatment of PSC, PBC, and NAFLD/NASH. Nonclinical in vitro pharmacology studies showed that CS0159 bound to FXR with a strong binding affinity and specificity, and induced FXR reporter gene expression. Nonclinical in vivo study in C57 mice showed that CS0159 strongly regulates the downstream target genes of FXR in the liver and ileum.

For efficacy study purposes, a STAM model of NASH was conducted in mice by a single subcutaneous injection of 200 μg streptozotocin (STZ) solution 2 days after birth and feeding with high fat diet (HFD; 57 kcal% fat) after 4 weeks of age. Model mice were orally administered with vehicle, CS0159 (0.04, 0.2, and 1 mg/kg) or reference compound telmisartan (10 mg/kg) once daily (QD) from 6 to 9 weeks of age.

Treatment with telmisartan showed significant decreases in NAFLD Activity Score (NAS) and fibrosis area compared with the vehicle group, indicating the drug successfully worked as a positive control in the study. Treatment with CS0159 at 0.04 mg/kg showed significant decreases in NAS score and the fibrosis area, and increasing trends in mean liver weight, mean liver-to-body weight ratio, and serum total cholesterol (TC) level, and decreasing trends in cytokeratin-18 (CK-18) score and plasma CK-18 level compared with the vehicle group. Treatment with CS0159 at 0.04 mg/kg tended to up-regulate bile salt export pump (BSEP) and SHP messenger RNA (mRNA) expression levels in the liver, and SHP and fibroblast growth factor 15 (FGF15) mRNA expression levels in the ileum, and down-regulate α-Smooth Muscle Actin (α-SMA), tumor necrosis factor α (TNF-α), and Stearoyl-coenzyme A Desaturase 1 (SCD1) mRNA expression levels in the liver compared with the vehicle group.

Treatment with CS0159 at 0.2 mg/kg showed significant increases in mean liver weight and mean liver-to-body weight ratio, significant decreases in the fibrosis area and CK-18 score, increasing trends in serum low-density lipoprotein cholesterol (LDL-C) level and liver TG content, and decreasing trends in NAS and plasma CK-18 level compared with the vehicle group. Treatment with CS0159 at 0.2 mg/kg showed significant up-regulation in BSEP and SHP mRNA expression levels in the liver, and SHP and FGF15 mRNA expression levels in the ileum, and a down-regulating trend in α-SMA mRNA expression level in the liver compared with the vehicle group.

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Treatment with CS0159 at 1 mg/kg showed significant increases in mean liver weight, mean liver-to-body weight ratio, and significant decreases in NAS, the fibrosis area, CK-18 score, and plasma CK-18 level compared with the vehicle group. Treatment with CS0159 at 1 mg/kg showed significant up-regulation in BSEP and SHP mRNA expression levels in the liver, and SHP and FGF15 mRNA expression levels in the ileum, a significant down-regulation in α-SMA mRNA expression level in the liver, and down-regulating trends in TNF-α and SCD1 mRNA expression levels in the liver, and apical sodium-dependent bile acid transporter mRNA expression level in the ileum compared with the vehicle group.

In summary, CS0159 significantly reduced the fibrosis area compared with the vehicle group, demonstrating an antifibrosis effect in the present study. CS0159 at 0.04 and 1 mg/kg significantly reduced NAS compared with the vehicle group. Among NAS, the CS0159 significantly reduced ballooning score compared with the vehicle group. Since hepatocyte ballooning is thought to be derived from oxidative stress-induced hepatocellular damage and is associated with disease progression of NASH (Fujii et al., 2009; Rangwala et al., 2011), it was suggested that CS0159 improved NASH pathology by inhibiting hepatocyte damage and ballooning cell formation.

A Phase I trial (CS0159-001) under IND 156038 is being conducted among healthy volunteers to assess the safety, tolerability, pharmacokinetic (PK), pharmacodynamics (PD), and food effect, including a single-ascending dose (SAD) study, multiple-ascending dose (MAD) study, and a pilot food effect study within the SAD study. The SAD and MAD studies were both randomized, double-blind, and placebo-controlled studies. The SAD study enrolled [redacted] at each predefined dose level [redacted], and continue the escalation until reaching the maximum tolerated dose or study termination rules, whichever comes first. All participants in SAD received the investigational drug or placebo in fasted state on Day 1, and then only patients of the second cohort received an additional dose of CS0159 or placebo in fed state followed by a washout period of 7 days. According to the data from the SAD study, MAD study was initiated with [redacted], and subjects received CS0159 or placebo for a consecutive 14 days, to assess the safety, tolerability, and PK/PD characteristics of CS0159 for a longer time.

The Phase I trial mentioned above was initiated with indication of PSC. All dose levels of SAD [redacted], including a pilot food effect assessment in the second level [redacted], and all dose levels of MAD [redacted] have already been completed. CS0159 was safe and well tolerated following a single oral dose of [redacted] to date.

In conclusion, pharmacology studies confirmed the treatment potential of CS0159 for the treatment of PSC and NAFLD/NASH by activating FXR and regulating its downstream signaling pathway. Adequate nonclinical safety evaluations of CS0159 were completed and revealed the test-article-related toxic effects.

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1.1. Study Rationale

The clinical utility of FXR agonism has been demonstrated by non-bile acid agonists, eg, tropifexor, cilofexor, TERN 101, EDP-305, MET-409, and nidufexor. Short-term studies have shown reduced liver fat content (LFC) and improved liver biochemistry as feasible endpoints. Pruritus and unfavorable changes in cholesterol profiles have somehow hampered FXR development and are often dose limiting. The risk-benefit profile of FXR agonists can be potentially enhanced through structural optimization resulting in potential differentiators for this class, such as a wider therapeutic index and/or a greater efficacy relative to existing candidates.

This Phase II study is designed to assess the safety, tolerability, PK, PD, and efficacy of CS0159 among NASH patients in the US.

1.1.1. Disease Information

NAFLD/NASH

Nonalcoholic fatty liver disease is the spectrum of liver disease in which hepatic steatosis, the macro-vesicular accumulation of TG in hepatocytes, develops in the absence of secondary causes, like medications, excessive alcohol consumption, or certain heritable conditions (Chalasani et al., 2018). Nonalcoholic fatty liver disease is the most common chronic liver disease in the US, with an estimation that about 25% of adults have NAFLD (American Liver Foundation: "NASH Definition & Prevalence,"). Nonalcoholic fatty liver disease can be categorized histologically into nonalcoholic fatty liver or NASH. Nonalcoholic steatohepatitis is the more aggressive form of NAFLD, with steatosis as well as evidence of hepatocyte injury and inflammation, with or without fibrosis. A meta-analysis reported that 7% to 30% of NAFLD patients who underwent voluntary liver biopsies had NASH, which indicated that the overall prevalence of NASH is between 1.5% and 6.45% (Younossi et al., 2016).

1.1.2. Farnesoid X Receptor Agonists

Many FXR agonists have been developed and are under nonclinical and clinical investigation. Obeticholic acid is one of the promising candidates. Obeticholic acid, developed by Intercept, has been approved for the treatment of PBC in combination with ursodeoxycholic acid, and is now being investigated for the indication of fibrosis due to NASH and PSC. Besides, another FXR candidate, cilofexor (formerly known as GS-9674) has initiated a Phase II trial of NASH and PSC patients, respectively. Tropifexor (also known as LJN452), sharing similar targets with CS0159, showed clinical benefits for NASH in Phase II clinical trials. As clinical evidence accumulates, these FXR agonists have confirmed the clinical potential for the treatment of PSC and NAFLD/NASH by activating FXR and regulating its downstream signaling pathway.

1.1.3. CS0159

1.1.3.1. Pharmacology

Pharmacodynamics studies showed that CS0159 bound to FXR with a strong binding affinity and specificity, and induced FXR reporter gene expression, with the median effective concentration (EC_{50}) values of 3.782 and 0.348 nM, respectively. CS0159 administration showed

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strong regulation for the downstream target genes of FXR in the liver and ileum of normal C57BL/6J mice, such as increasing the expression of SHP and BSEP in the liver, and SHP and FGF15 in the ileum, and reducing the expression of CYP7A1 in the liver, which suggested that CS0159 may be involved in metabolic regulation by changing the FXR signaling pathway.

In a STAM model of NASH induced in C57BL/6J male mice by STZ and HFD, CS0159 administration significantly reduced liver NAS, fibrosis and CK-18 score, and plasma CK-18 level in a dose-dependent manner with a lowest effective dose of 0.04 mg/kg. CS0159 also showed significant up-regulation or up-regulation tends in BSEP and SHP mRNA expression levels in the liver, and SHP and FGF15 mRNA expression levels in the ileum, and significant down-regulation or down-regulation tends in α-SMA, TNF-α, and SCD1 mRNA expression levels in the liver, and ASBT mRNA expression level in the ileum in a dose-dependent manner. In another NASH C57BL/6J mouse model induced by HFD and carbon tetrachloride, administration of CS0159 significantly reduced TC and LDL-C levels in serum, TG, fibrosis, NAS, collagen-1 alpha and α-SMA mRNA expression levels in the liver, and increased SHP mRNA expression level in the liver, and FGF15, BSEP, and SHP mRNA expression levels in the ileum, with a lowest effective dose of 0.04 mg/kg.

Safety pharmacology studies showed that CS0159 had no effect on the central nervous system and respiratory system of Sprague Dawley rats (when administered at 0.3, 1.5, and 10 mg/kg), or the cardiovascular system of beagle dogs when administered at 0.1→0.5→2 mg/kg. The half maximal inhibitory concentration (IC_{50}) value for the inhibitory effect of CS0159 on the human ether-à-go-go-related gene potassium current was 1.36 μM.

For further details about nonclinical studies, please refer to the CS0159 investigator's brochure (IB).

1.2. Benefit-risk Assessment

The study may provide individual and general benefits.

This study will include patients with nonalcoholic NASH. There is a potential benefit to the patients participating in this study. In general, the study has the potential benefit to safely reduce liver steatosis, inflammation, and fibrosis in patients with nonalcoholic NASH with the daily administration of CS0159 (Linafexor; 1.4 mg or 2 mg).

Based on the CS0159 benefit/risk assessment, no impact is anticipated and the existing safety monitoring and management guidelines, and risk mitigation measures provided in the study protocol and related study documentation are considered adequate.

Based on the available safety data from the Phase I study, no expected suspected adverse events (AEs) with CS0159 have been identified to date.

Coronavirus Disease 2019 Pandemic

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Coronavirus Disease 2019 (COVID-19) testing will be conducted per local procedures/guidelines if the patient has specific symptoms or is suspected of being infected during the conduct of this study.

The safety monitoring and risk mitigations defined in this study protocol and related study documents have taken into consideration the additional potential impacts of the COVID-19 pandemic if still active during the conduct of this study.

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2. OBJECTIVES, ENDPOINTS AND ESTIMANDS

2.1. Objectives

The primary objectives of the study are:

Safety

- To evaluate the safety and tolerability of CS0159 in patients with NASH treated over 12 weeks.

Efficacy

- To assess the changes in liver steatosis through magnetic resonance imaging (MRI) proton density fat fraction (PDFF) from baseline to Week 12.

The secondary objectives of the study are:

Pharmacokinetics (PK) and pharmacodynamics (PD)

- To assess the PK and PD profiles of CS0159.

Efficacy

- To assess the changes in inflammation changes in alanine aminotransferase (ALT) levels from baseline to Week 12.

The exploratory objectives of the study are:

- To explore the changes in liver steatosis, inflammation, and fibrosis through a set of target biomarkers from baseline to Week 12.
- To explore changes in inflammation through iron-corrected T1 (cT1) from baseline to Week 12.
- To explore the dose-response relationship of CS0159 on markers of hepatic steatosis, inflammation, and fibrosis in NASH from baseline to Week 12.
- To explore the dose-response relationship of CS0159 on metabolic markers.

2.2. Endpoints

The primary safety endpoints of the study are:

- Incidence and severity of AEs/treatment-emergent AEs (TEAEs).
- Incidence and severity of adverse drug reactions.
- Clinical laboratory assessments (hematology, biochemistry, urinalysis, and hematopoietic and coagulation markers).

The primary efficacy endpoint is:

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- The LFC as measured by MRI-PDFF mean changes from baseline to Week 12.

The secondary PK/PD endpoints of the study are:

Pharmacokinetics:

- Pharmacokinetic parameters of unchanged CS0159, including but not limited to the area under the concentration-time curve (AUC; $AUC_{0-\infty}$, AUC_{0-last}, $AUC_{0-\tau}$), maximum concentration (C_{max}), time to maximum plasma concentration (t_{max}), half-life ($t_{1/2}$), and accumulation ratio of AUC in plasma.

Pharmacodynamics:

- Plasma concentrations and PD parameters of the biomarkers of FXR target engagement FGF19 and serum 7α-hydroxy-4-cholesten-3-one (C4) from baseline to Week 12.

The secondary efficacy endpoints of the study are:

- The proportion of patients with ≥30% reduction in liver fat through MRI-PDFF from baseline to Week 12.
- The ALT mean changes from the baseline to Week 12.
- The proportion of patients having a ≥30% reduction in ALT levels from the baseline to Week 12.

The exploratory endpoints of the study are the mean changes from baseline to Week 12 in:

- Inflammatory and fibrosis biomarkers (alkaline phosphatase [ALP], aspartate aminotransferase [AST], gamma-glutamyl transferase (GGT), platelet count, CK-18), procollagen C3, and enhanced liver fibrosis (ELF, namely tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid).
- The proportion of patients with cT1 mapping ≥880 ms at the baseline having a ≥80 ms (milliseconds) reduction in cT1 levels.
- Metabolic biomarkers (fasting glucose, insulin, Homeostatic Model Assessment for Insulin Resistance [HOMA] index, hemoglobin A1c, and bile acids).
- Standard lipid panel (TC, calculated LDL-C, high-density lipoprotein cholesterol [HDL-C], and TGs).
- Lipid profile (nuclear receptor and metabolism-altering mechanisms of action).
- Insulin sensitivity index (lipoprotein insulin resistance index based on 6 lipoprotein parameters).
- Lipoprotein particle concentration and size including LDL-P and HDL-P.
- GlycA and branched-chain amino acid concentrations.
- Bile acids profile (total), and C4 (an intermediate in the synthesis of bile acids from cholesterol and a biomarker of hepatic CYP7A1 activity).

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Potential posthoc analysis:

- NIS-4 (NASHnext): Serum will be saved for potential posthoc analysis of NIS-4 changes from baseline to Week 12 after the last dose of study intervention.

2.3. Estimands

In line with International Council for Harmonisation (ICH) E9 (R1) addendum, 5 attributes (treatment, population, endpoint, intercurrent events, and population-level summary) will be specified to translate the primary and key secondary efficacy objectives into treatment effects that are to be estimated (estimands). The treatment conditions of interest are CS0159 1.4 mg administered daily, and CS0159 2 mg administered daily, and are compared with a matching placebo administered daily. The treatment effect is assessed by the primary endpoint of improvement in LFC. The population of patients targeted is adults with NASH. Intercurrent events will be handled through a combination of treatment-policy strategy and composite strategy. The population-level summary of the treatment effect will be quantified by modeling the change in LFC and comparing least squares means of active doses to placebo.

Full details of intercurrent event strategies and quantification of endpoints will be given in the statistical analysis plan (SAP).

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3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

This will be a multicenter, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, PK, and efficacy of CS0159 in the treatment of patients with NASH over 12 weeks.

Potential patients will be screened from Day -56 to Day -1 to assess their eligibility to enter the study. Imaging biomarkers noninvasive testing (NIT) will be performed through MRI-PDFF and cT1, but no liver biopsy.

Additionally, patients enrolled at a site with the capability to conduct magnetic resonance elastography (MRE) will have the option to undergo the MRE testing at the screening period and at Week 12 of this study.

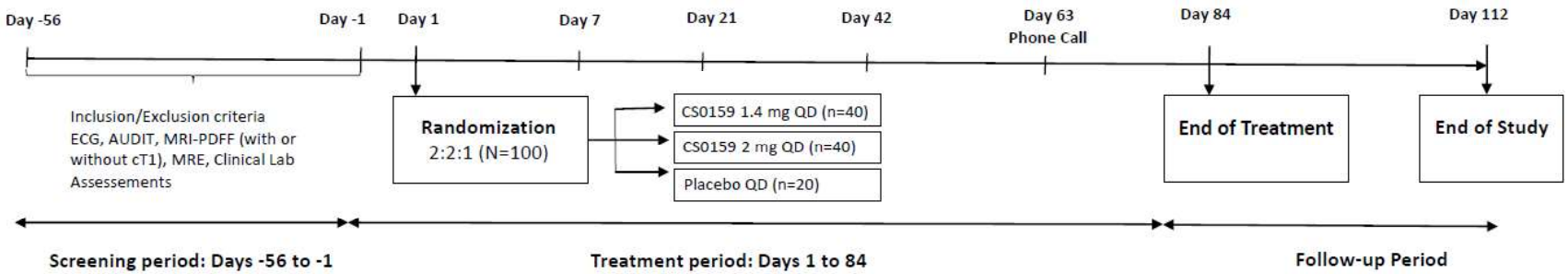
Patients will be randomized in a 2:2:1 ratio using an interactive web response system (IWRS) to receive matching CS0159 1.4 mg or 2 mg, or placebo tablets QD, respectively. Randomization will be stratified by diabetes status. The diabetic patients will be evenly distributed among the patient groups.

On Day 1, the following assessments will be performed predose: physical examination, urine pregnancy test, vital signs, wet biomarkers, PK/PD assessments, and pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale). In addition, clinical laboratory assessments will be performed on Day 1.

There will be a total of up to 8 visits to the clinical site and 1 phone call visit on Week 9, including up to 2 screening visits; IWRS randomization on Day 1; and visits on Day 7 (Week 1), Day 21 (Week 3), Day 42 (Week 6), Day 63 (phone call at Week 9), and Day 84 (Week 12). A final safety follow-up visit will occur on Day 112 (Week 16).

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Figure 1: Study Design



Abbreviations: AUDIT = alcohol use disorders identification test; cT1 = iron-corrected T1; ECG = electrocardiogram; MRE = magnetic resonance elastography; N = number of patients; MRI-PDFF = magnetic resonance imaging proton density fat fraction; QD = once daily.

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

Study Population: CS0159 is being developed for the treatment of patients with NASH.

Study design: This study is a randomized, double-blind design to ensure the balance of study populations, avoid system differences between test and control groups, and to minimize potential bias resulting from differences in treatment and management.

Sample size: The sample size of 40 patients per active dose group with 20 patients in the placebo group would provide 80% statistical power under the following assumptions:

- $\alpha = 0.05$, 2-sided test.
- Placebo mean % Δ from baseline in LFC = -10%, active mean % Δ from baseline in LFC = -25%.
- Common standard deviation= 19%.

Control group: This will be a placebo-controlled study as there is no approved drug for this disease. Placebo is chosen as the control drug to control all potential effects on the actual or apparent disease progression other than those arising from the pharmacological effect of the study drug (eg. Natural course of the disease, expectation of patients or investigators, effects of participating in a study, use of other treatment, subjective factors on assessment; ICH E10, 2001).

3.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the study.

3.4. Selection of Doses in the Study

This Phase II study will consist of 3 arms: 2 dose levels of CS0159 (1.4 mg QD and 2 mg QD) and 1 placebo QD arm.

The selection of doses for this study is based on integration of toxicology and PK data from nonclinical studies and safety and PK data from the Phase I clinical study (Study CS0159-001).

The no-observed-adverse-effect level (NOAEL) for CS0159 in a 13-week toxicology study in rats was considered 0.3 mg/kg/day, with the corresponding exposure ($AUC_{0\text{-}24h}$) of 88.4 h*ng/mL for males, and 160 h*ng/mL for females. The NOAEL for CS0159 in a 13-week toxicology study in dogs was considered 0.06 mg/kg/day in males and 0.03 mg/kg/day in females. The corresponding exposure ($AUC_{0\text{-}24h}$) for males and females was 172 and 59.3 h*ng/mL, respectively. The exposure at the NOAEL in toxicology studies in animals provides >3.6 × safety margin to the human exposure of CS0159 at 2 mg, which is 16.6 h*ng/mL.

In Study CS0159-001, CS0159 was well tolerated at single doses [redacted] and at multiple doses [redacted] to date. No pruritus or serious adverse event (SAE) occurred. Following single doses, $AUC_{0\text{-}\infty}$ increased in a dose-proportional manner over the [redacted]

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[redacted]dose. The less than proportional increase of exposure is observed over[redacted] dose, which may be caused by between-patient variability and the small number of patients. AUC_{0-24} increased in a dose-proportional manner following multiple doses over the[redacted] The $t_{1/2}$ is approximately[redacted] following both single and multiple doses. No significant drug accumulation was observed following consecutive dosing for 14 days. The t_{max} and $t_{1/2}$ are similar in both the fed and fasted states. Food reduced C_{max} by approximately[redacted] and increased $AUC_{0-\infty}$ by approximately[redacted] compared to the fasted state. The pharmacodynamic marker, FGF19 continues to rise with increasing doses up to[redacted] in the SAD study and[redacted] in MAD study, and appears to have reached plateau after single of multiple doses of[redacted]. The multiple doses of[redacted] increased FGF19 by approxim[redacted]. To explore doses with a greater FGF19 elevation[redacted] are selected to provide potential pharmacological effects and clinically relevant changes with relatively good safety profile.

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4. SELECTION OF STUDY POPULATION

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

4.1. Inclusion Criteria

Patients must satisfy all of the following criteria at screening unless otherwise stated:

1. Patients capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.
2. Male and female patients of any ethnic origin aged 18 to 75 (inclusive) at the time of the ICF signature.
3. Patients who meet at least 1 of the following criteria for the diagnosis of NASH:
    a) Biopsy-proven NASH within 12 months of screening, defined by the NASH Clinical Research Network (NASH CRN) Histologic Scoring System: NAFLD activity score (NAS) ≥4 (with ≥1 point in each component of steatosis, lobular inflammation, and hepatocellular ballooning) AND stage 1, 2, or 3 fibrosis.
    b) Evidence of liver fat distribution ≥8% via MRI-PDFF within 3 months of screening.
4. Evidence of metabolic syndrome defined by the presence of at least 3 of the below criteria, except for those patients with biopsy-proven NASH:
    a) Waist circumference over 40 inches (men) or 35 inches (women).
    b) Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or on drug treatment for hypertension is an alternate indicator.
    c) Fasting TG level ≥150 mg/dl or on stable and permitted drug treatment for elevated TG.
    d) Fasting HDL-C level <40 mg/dl (males) or <50 mg/dl (females) or on drug treatment for reduced HLD-C.
    e) Fasting glucose levels ≥100 mg/dl or on stable and permitted drug treatment for elevated glucose.
5. Body mass index (BMI) >25 kg/m^2, NOTE: for Asian-Americans BMI >23 kg/m^2.
6. Stable use of other antidiabetic, weight loss, or lipid-modifying medications for at least 12 weeks prior to randomization.
7. Patients who agree to abstain from heterosexual activity, use adequate hormonal contraception, or use highly effective double barrier contraception (ie, a combination of condom or diaphragm AND hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system or documented vasectomy) during the study and for 12 weeks after the last dose of the study intervention, unless:
    a) Patient is a female of nonchildbearing potential, defined as a woman who had surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) at least 3 months before screening OR postmenopausal woman ≥45 years of age with >1 year since last menstrual period.

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b) Patient is a surgically sterilized male through vasectomy or bilateral orchiectomy at least 3 months before screening.

8. For women of childbearing potential, a negative serum pregnancy test at screening is to be conducted and must have a urine pregnancy test within 24 hours before the first dose of the investigational product (IP).
9. Male patients with female partners of childbearing potential should agree to use highly effective contraceptive measures from the screening visit through 12 weeks after the last dose of study drug. Highly effective contraceptive measures include documented vasectomy, abstaining from sexual intercourse, and double-barrier method (please see exclusion criterion 7). As there may be a risk of IP being secreted in the ejaculate, male patients (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and 12 weeks after the last dose of study drug. Male patients with female partners that are confirmed as postmenopausal are not required to use contraceptive measures.

4.2. Exclusion Criteria

Patients will be excluded from the study if they satisfy any of the following criteria at screening unless otherwise stated:

The following are the main exclusion criteria:

1. History of hypersensitivity to the IP or its excipients or drugs of similar chemical classes.
2. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
3. Previous exposure to FXR agonists 3 months prior to the first dosing.
4. Current or within 6 months of screening use of drugs associated with steatosis, including but not limited to eg, methotrexate, amiodarone, high-dose estrogen, tamoxifen, long-term systemic steroids, anabolic steroids, valproic acid.
5. Prothrombin time international normalized ratio >1.3, unless due to therapeutic anticoagulation.
6. Total bilirubin >upper limit of normal (ULN; except for patients with Gilbert's syndrome with a normal direct bilirubin value and normal reticulocyte count).
7. Platelet count <140 000/mm³, absolute neutrophil count <1500 cells/mm^3, or total white blood cells <3000 cells/mm^3.
8. Alanine aminotransferase and AST >5 × ULN, or ALP >1.5 × ULN.
9. Weight changes >10% in 6 months prior to screening, or weight changes >5% from the screening MRI-PDFF to randomization or from the time of the diagnostic liver biopsy to randomization, whichever is longer.
10. Poorly controlled hypertension (systolic >160 mm Hg, or diastolic blood pressure >100 mm Hg – mean of 3 measurements).
11. Uncontrolled diabetes mellitus (hemoglobin A1c >10.0% during screening).

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12. Cirrhosis of the liver as defined by any of the following:
    a) Cirrhosis on historical liver biopsy (eg, Brunt/Kleiner Stage 4 or equivalent).
    b) Evidence of cirrhosis on liver imaging (eg, ultrasound, computed tomography, or MRE) including a nodular liver surface, splenomegaly, or portal venous collaterals.
    c) History of decompensated liver disease (ascites, hepatic encephalopathy, variceal bleeding).
13. Any of the following:
    a) History of or positive for human immunodeficiency virus (HIV) at screening.
    b) Chronic hepatitis B virus infection (hepatitis B surface antigen positive). For patients who are negative for HBsAg but are positive for either surface antibodies and/or core antibodies, HBV DNA polymerase chain reaction will be performed and if any test result meets or exceeds detection sensitivity, the patient will be excluded.
    c) Chronic hepatitis C virus (HCV) infection (HCV antibody (HCVAb) and HCV RNA quantification positive). If the patient is HCVAb positive, then HCV RNA quantification by reverse transcription polymerase chain reaction (RT-PCR) will be performed. If the HCV RNA quantification is positive, then the patient will be excluded. Patients cured of HCV infection less than 2 years prior (based on the date of RNA PCR negative confirmation following the conclusion of treatment) to the screening visit are not eligible.
14. History of acute liver complications due to gallstones (eg, acute cholecystitis or acute biliary obstruction) unless the patient has had a cholecystectomy (more than 3 months prior to screening).
15. History of liver transplantation or causes of liver disease other than NASH, such as alcoholic liver disease, PBC, PSC, autoimmune hepatitis, Wilson disease, iron overload, alpha-1-antitrypsin deficiency, drug-induced liver injury, known or suspected hepatocellular carcinoma.
16. Patients with contraindications to MRI imaging include:
    a) Brain aneurysm clip.
    b) Implanted neural stimulator.
    c) Implanted cardiac pacemaker or defibrillator, or presence of intracardiac wires.
    d) Prosthetic heart valves.
    e) Cochlear implant.
    f) Ocular foreign bodies that might be ferromagnetic (eg, metal shavings).
    g) Other implanted medical devices (eg, insulin pumps).
    h) Metal shrapnel or bullets still in the body.
    i) Severe claustrophobia.
    j) Tattoos (as determined by the investigator and imager).
    k) Weight in excess of MRI machine capacity.
17. Pregnant or nursing (lactating) women.
18. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is

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defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the Alcohol Use Disorders Identification Test questionnaire ≥8.

19. Inability to reliably quantify alcohol consumption based on local study team's judgment.
20. History or evidence of ongoing drug abuse, within the last 6 months prior to randomization. Marijuana or cannabidiol use is not allowed if it is determined to be medically inappropriate by the investigator.
21. History or presence of any disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the large intestine, eg, inflammatory bowel disease, prior or planned (during the study period) bariatric surgery (such as gastroplasty, roux-en-Y gastric bypass).
22. Body mass index >50 kg/m^2.
23. Estimated glomerular filtration rate (eGFR) ≤60 ml/minute/1.73m2 (calculated by the modification of diet in renal disease equation for the eGFR (MDRD)).
24. History or presence of chronic pruritus that is defined as pruritus lasting 6 weeks or more prior to the enrollment of the study.
25. Clinically significant ECG abnormalities or the corrected QT interval by Fridericia (QTcF) greater than 450 ms for males and 470 ms for females at either screening or baseline, or any prior history of QT abnormality.
26. Concomitant use of medications, food, and drinks that are strong or moderate CYP3A4 inhibitors or inducers within 14 days prior to the first dose of study drug and throughout the study duration.
27. Concomitant medications: vitamin E ≥800 IU/day, thiazolidinediones, glucagon-like peptide-1 agonists (unless the subjects on a stable dose of GLP1a for diabetes mellitus ≥ 6 months before screening), sodium-glucose transport protein 2 inhibitors, and unstable dose (dose changes >30% in the last 30 days prior to screening) of insulin.
28. Any other condition(s) (including cardiovascular diseases) that would compromise the safety of the patient or compromise the quality of the clinical study, as judged by the investigator.
29. Initiated a structured weight loss or dietary program (eg. Weight Watchers, Jenny Craig, physician prescribed program) within 3 months prior to randomization.
30. Initiated treatment with medications for weight loss within 6 months prior to randomization.
31. Patients with a history or diagnosis of:
    a) Solid organ transplantation and hematopoietic transplantation
    b) Multiple endocrine neoplasia (MEN I or MEN II)

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4.3. Discontinuation Criteria

4.3.1. Screen Failures

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

Patients who do not meet the criteria for participation in the study due to transient conditions (eg, medical conditions or laboratory abnormalities) and can be repeated within the screening window, may retest under the same patient number as an unscheduled visit. However, if the transient condition requires the patient to wait longer than the screening period, the patient may rescreen once. Rescreened patients will sign a new ICF and will be assigned a new patient number (different than that assigned at the initial screening). All screening procedures would be repeated except the MRI-PDFF, cT1 and / or MRE, if within 3 months from the last results.

Patients who do not meet the criteria for participation in this study may be rescreened.

4.3.2. Discontinuation of Study Treatment

For any patient who decides to withdraw from the study, the investigator should inquire about the reason for withdrawal, request that the patient to return all unused IP(s), request that the patient return for end of treatment (EOT) visit, if applicable, and follow-up with the patient regarding any unresolved AEs. Although a patient may discontinue study treatment, every effort must be made to continue the patient on the study, returning for the EOT visit (if prematurely discontinuing treatment) and the safety follow-up visit.

If a patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. Sponsor may retain and continue to use any data collected before such withdrawal of consent. Additionally, patients may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. Refer to the Schedule of Assessments (Appendix 5) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

For safety monitoring purposes, patients who withdraw after receiving study drug should return to the site as soon as possible and undergo the EOT evaluations. Patients should then return for the safety follow-up assessments after the last dose of study drug. Any patient who withdraws with ongoing AEs/SAEs should be followed until resolution of their AE(s) or until the investigator has determined that the AE(s) has stabilized.

Site personnel will attempt to contact any patient who does not return to the clinic for the scheduled visit at least 3 times using the patient's preferred method of communication, followed by a certified letter if the 3 attempts are unsuccessful. Any patient who still cannot be reached following those attempts will be considered lost to follow-up. These patients will be included in the analysis.

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Patients may be discontinued from the study at any time if the patient, investigator, or sponsor determines that it is not in the best interest of the patient to continue participation.

Discontinued patient will be asked to complete Week 12 as an early termination and will return for Week 16 follow-up visit. PK/PD assessment will be not collected.

Reasons for treatment discontinuation and withdrawal may include, but are not limited to:

- Adverse events requiring discontinuation (ie, AEs that may jeopardize patient's health or may compromise study objectives based on the investigator's clinical judgment).
- Postbaseline elevations in liver transaminase levels (ALT or AST >3 × ULN, accompanied by total bilirubin >2 × ULN OR international normalized ratio >1.5, confirmed by repeated assessments 24 hours apart).
- Noncompliance with study drug dosing or study procedures.
- Pregnancy in female patients.
- Important protocol deviation (ie, affecting the patient's safety, treatment with any prohibited concomitant medication) as judged by the investigator.
- Investigator or sponsor determines it is in the best interest of the patient.
- Patient withdrawal of consent.
- Patient lost to follow-up.
- Death.
- Study termination.

The primary reason for premature treatment discontinuation of study treatment or study withdrawal should be documented on medical records and appropriate electronic case report form (eCRF).

4.3.3. Individual discontinuation criteria

Below are listed individual discontinuation criteria:

• CTCAE Grade 3 or higher event that is possibly or probably related to the study drug OR

• CTCAE Grade 4 or higher regardless of attribution to study drug

• Drug-induced liver injury (DILI), see details in Appendix 4

• In the opinion of the investigator, the continuing in the study is not in the best interest of the patient.

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In addition, any patient has the right to voluntarily withdraw from the study at any time for any reason. Investigators have the right to withdraw a patient from the study at any time. Reasons for patient discontinuation from the study may include, but are not limited to, the following:

• Patient withdrawal of consent

• Study termination or site closure

• Adverse event

• Loss to follow-up

• Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor.

Every effort will be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. Patients who withdraw the study will participate at the end of the treatment visit at the time of discontinuation.

4.3.3.1. Liver Injury

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a patient meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the patient.

Suggested actions and follow-up assessments can be found in Appendix 4.

4.3.4. Lost to Follow-up

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

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

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

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

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

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4.3.5. Follow-up of Patients Prematurely Discontinued from the Study Treatment Regimen or Withdrawn from Study

Patients who discontinue from the study will be asked to complete the final study procedures (Week 12 visit). All AEs and SAEs that are ongoing at the time of discontinuation will be followed for 30 days, or until resolution, or until the investigator has determined that the AEs and SAEs have stabilized.

4.4. Study Termination

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

- Adverse events unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of drug development.

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

- Failure of the investigator to comply with the protocol, the requirements of the institutional review board/ethics committee or local health authorities, the sponsor's procedures, or good clinical practice guidelines
- Inadequate recruitment of patients by the investigator.

4.4.1. Study Stopping Rules

- If 1 patient meets Grade 5 CTCAE
- If 2 patients experience same Grade 4 CTCAE
- If 3 patients meet same Grade 3 CTCAE

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If any of the above criteria are met, then pause the enrollment of patients in the study. The data monitoring committee (DMC) should assess the causality of these events. Only if the events are deemed by the DMC as unrelated to study drug use, then the study enrolled could be restarted. Further details regarding the DMC in Section 7.9.3.

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5. STUDY TREATMENTS

5.1. Treatments Administered

Study Treatment Name:	CS0159 1.4 mg	CS0159 2 mg	Placebo
Dosage Formulation:	Blue film-coated tablet	Blue film-coated tablet	Blue film-coated tablet
Unit Dose Strength(s):	CS0159: 1.4 mg	CS0159: 2 mg	Placebo: 0 mg
Route of Administration:	Oral	Oral	Oral

Abbreviations: QD = once daily

5.2. Preparation, Storage, Handling, and Accountability

Study drug (CS0159 or placebo) will be administered by patients orally QD, in the morning before breakfast, approximately the same time each day. For site visits on Days 1, 42, and 84, doses will be administered only after blood collection for PK and PD assessments.

Matching CS0159 (1.4 mg or 2 mg tablet) and placebo tablets will be provided to patients in prepackaged single dose kits, identical in appearance, according to the randomization schedule. From Days 1 to 84, each patient will take a total of 1 tablet per day, as follows:

- CS0159 1.4 mg group will receive: 1 × 1.4 mg CS0159 tablet QD daily
- CS0159 2 mg group will receive: 1 × 2 mg CS0159 tablet QD daily
- Placebo group will receive: 1 × placebo tablet QD daily.

The study drug will be supplied by the sponsor (or designee), along with the batch numbers and certificates of analysis. The study drug will be provided in bottles containing individual patient kits. Two bottles will be assigned to the patient on Day 1 and 2 additional bottle on Day 42 (Week 6).

Patients allocated in the 1.4-mg dose group will receive 2 bottles with CS0159 tablets at 1.4 mg that will have enough tablets to cover 6 weeks plus 18 days. Patients will be informed of the importance to take 1 tablet QD daily.

Patients allocated in the 2-mg dose group will receive 2 bottles with CS0159 tablets at 2 mg that will have enough tablets to cover 6 weeks plus 18 days. Patients will be informed of the importance to take 1 tablet QD daily.

Patients allocated in the placebo group will receive 2 bottles with placebo tablets that will have enough tablets to cover 6 weeks plus 18 days. Patients will be informed of the importance to take 1 tablet QD daily.

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Drug administration should be at a consistent time each day (ie, separated by approximately 24 hours [±2 hours]). The patient will keep a daily diary to record the drug administration compliance. Doses that are late by more than 12 hours should not be taken and recorded in the dosing diary as missed.

The bottle's labels will all look the same except for the randomization numbers on the bottles that will match the randomization codes.

All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. The storage condition of the study drug is controlled at room temperature 15°C to 25°C, protected from light. All details about the drug preparation, storage, handling, and accountability will be fully described in the Pharmacy Manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

5.3. Method of Treatment Assignment

All patients will be centrally randomized using an IWRS. Before the study is initiated, all information and directions for the system will be provided to each site.

On Day 1, patients will be assigned a unique number (randomization number) in ascending numerical order at each study site. The patient number encodes the patient's assignment to 1 of the 3 arms of the study, according to the randomization schedule. Each patient will be dispensed blinded study treatment, labeled with his/her unique randomization number, throughout the study. Study treatment will be dispensed at the study visits summarized in the Schedule of Assessments (Appendix 5).

Returned study treatment should not be re-dispensed to the patients.

5.3.1. Dose Modification

Dose reductions will not be allowed. If a dose reduction is needed, the patient should be discontinued from treatment and all EOT assessments completed.

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5.4. Blinding

This is a double-blind, placebo-controlled study. All study personnel and patients will be blinded to the assigned study treatment with the exception of specific personnel as described in a separate maintaining study blind and unblinding plan.

Matching CS0159 or placebo tablets will be provided to patients to ensure treatment blinding.

Unblinding should only occur in the event of a medical emergency, given that the knowledge of the study drug is essential for the clinical management or welfare of the patient. Unblinding will be performed via the IWRS. In the event of emergency unblinding by the investigator, the sponsor must be informed as soon as possible.

5.5. Treatment Compliance

The investigator (or designee) must maintain accurate records of all study treatments, including dates of study drug receipt, quantities dispensed to and returned, and batch/lot numbers.

For study drug administration at site (during assessment visits on Days 1, 42, and 84), the date and time of administration will also be documented in the patient's source records.

Significant treatment noncompliance and/or inability or unwillingness to follow instructions given by study personnel, as assessed by the investigator, might lead to patient exclusion from the study.

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6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapy

Any NASH-related medication taken within 6 months prior to first screening visit and all other ongoing medications at signing of the ICF (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study should be recorded in the source documents and eCRF along with:

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Patients should be discouraged from starting any new medication, both prescribed and over-the-counter, and/or herbal supplements without consulting the investigator unless the new medication is required for emergency. Use of any newly prescribed, intermittent, or as-needed medication taken by a patient during the study and its reason for use will be documented in the source documents and eCRF.

In general, patients will be expected to continue concomitant treatments for stable or controlled concurrent medical conditions, provided those treatments are permitted by the protocol.

Female patients may be in use of the following hormonal contraception methods at enrolment and must maintain stable doses throughout the treatment and follow-up period:

- hormonal contraception associated with inhibition of ovulation, intrauterine device, or intrauterine hormone-releasing system.

Patients will not participate in any other investigational study drug trial in which receipt of any investigational drug occurred within 30 days or 5 × the respective half-life, whichever is longer, prior to enrollment and during the entire study.

Patients are not permitted to take the following drugs also specified in the exclusion criteria during the study (Section 4.2):

- Drugs associated with steatosis including but not limited to: amiodarone, methotrexate, tamoxifen, high-dose estrogen, valproic acid, obeticholic acid, elafibranor systemic (oral, parenteral) glucocorticoids, fluoxetine. Less likely: chlorpromazine risperidone, olanzapine, venlafaxine, tianeptine, imipramine.

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Statins drugs (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) unless under stable usage for more than 1 month. In addition, due to the short half-life of CS0159, statins can be used 2 hours after CS0159.

- Drugs that are strong or moderate CYP3A4 inhibitors or inducers within 14 days prior to the first dose of study drug and throughout the study duration including but not limited to:
    - Strong inhibitors: ceritinib, clarithromycin, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, ribociclib, ritonavir, saquinavir, telithromycin, tucatinib, voriconazole.
    - Moderate inhibitors: aprepitant, crizotinib, diltiazem, erythromycin, fluconaaloe, grapefruit juice, netupitant/palonosetrc, verapamil.
    - Inducers: Barbiturates, brigatinib, carbamazepine, clobazam, dabrafenib, efavirenz, elagolix, enzalutamide, eslicarbazepine, glucocorticoids, letermovir, lorlatinib, modafinil, nevirapine, oxcarbazepine, perampanel, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, telotristat, troglitazone.
- Vitamin E ≥800 IU/day.
- Thiazolidinediones.
- Glucagon-like peptide-1 agonists (unless the subjects on a stable dose of GLP1a for diabetes mellitus ≥ 6 months before screening, and keep on a stable dose thereafter).
- Sodium-glucose transport protein 2 inhibitors.

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7. STUDY ASSESSMENTS AND PROCEDURES

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

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol specified criteria and will be performed within the timeframe defined in the Schedule of Assessments.

7.1. Screening Procedures (Days -56 to -1)

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. All eligibility laboratory assessments will be conducted centrally.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screen failure (see Section 4.3.1), as applicable.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed volumes as stated by local regulations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Patients will undergo study-specific screening within 56 days prior to first administration of the study drug (Day 1). Patients will sign the study ICF in the presence of the investigator (or appropriate designee), prior to any screening procedures being performed.

A paper questionnaire will be provided to all patients on the first screening visit, along with instructions and appropriate training for its use.

This study will have up to 2 screening visits. During the screening visits (Days -56 to -1), the following procedures or assessments will be performed:

- Demographic data
- Medical history
- Prior and concomitant medications, including all prior medications taken within 6 months prior to first screening visit and all concomitant medications

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- Inclusion/exclusion criteria (eligibility review)
- Hepatitis A virus (anti-HAV), HBsAg, HCV, and HIV (anti-HIV) test
- Serum pregnancy test
- Alcohol Use Disorders Identification Test (AUDIT)
- Imaging biomarkers NITs: MRI-PDFF and cT1(cT1 testing applies only for those patients who meet inclusion criteria and will be enrolled in this study)
- Magnetic resonance elastography testing will be performed only in patients enrolled at a site with capacity to conduct MRE
- Physical examination
- 12-lead ECG. Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording ECGs and vital signs
- Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature. Temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study
- Clinical laboratory assessments: biochemistry, hematology, urinalysis, and coagulation. Biochemistry includes hemoglobin A1c, ALT, AST, ALP, GGT, lactate dehydrogenase (LDH), creatine kinase, total and direct bilirubin, total protein, albumin, globulin, blood urea nitrogen (BUN), creatinine, eGFR, uric acid, amylase, sodium, potassium, calcium, magnesium, chloride, fasting glucose, TGs, TC, LDL-C, HDL-C, bile acids. Hematology includes complete blood cell count with differential (red blood cells, white blood cells, platelets, hemoglobin, and hematocrit). Coagulation includes prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and fibrinogen. Urinalysis includes analysis of protein, glucose, ketones specific, blood, specific gravity, pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine while blood cells.

7.2. Study Site Admission and Randomization (Day 1)

Patients will be randomized on the same day of first dose of the study drug (Day 1). On arrival at the study site on Day 1, the following procedures or assessments will be performed prior to dosing:

- Concomitant medications record
- Inclusion/exclusion criteria (eligibility review)
- Serum/urine pregnancy test (within 24 hours before the first dose of study intervention)

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- Wet biochemical NITs for NASH including: ALT, AST, ALP, platelet count, GGT, fasting glucose, hemoglobin A1c, TGs, TC, LDL-C, HDL-C, CK-18 (M65), procollagen C3, and HOMA index. Additional samples will be collected and stored for potential posthoc analysis of NIS-4

- Intense PK/PD assessments will be performed in subgroups (ie, n= from 30 to 40 patients). The sampling timepoints include predosing (0 hour up to 30 minutes before dosing) and postdosing 0.5 ± 3 minutes, 1 ± 5 minutes, 1.5 ±10 minutes, 2 ± 10 minutes, 3 ± 15 minutes, and 5 hours ± 15 minutes, which will be performed before lunch. Three collections PK/PD sampling will be performed in patients not participating in the PK/PD subgroup. The sampling timepoints will include predosing of 0 hour up to 30 minutes before dosing and postdosing of 1±0.5 hour and 4 hours ± 15 minutes, which will be performed before lunch. The predosing will be performed before the breakfast (low fat/sugar-diet breakfast), which will be arranged before 0.5-hour postdose.

- Interactive web response system randomization
- Physical examination
- Alcohol Use Disorders Identification Test (AUDIT)
- Patient will be asked about any changes in alcohol consumption
- Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature. Temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study. Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording vital signs
- Pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale)
- Clinical laboratory assessments (will be performed on Day 1): biochemistry, hematology, urinalysis, and coagulation. Biochemistry includes hemoglobin A1c, ALT, AST, ALP, GGT, LDH, creatine kinase, total and direct bilirubin, total protein, albumin, globulin, BUN, creatinine, eGFR, uric acid, amylase, sodium, potassium, calcium, magnesium, chloride, fasting glucose, TGs, TC, LDL-C, HDL-C, bile acids. Hematology includes complete blood cell count with differential (red blood cells, white blood cells, platelets, hemoglobin, and hematocrit). Coagulation includes PT, PTT, INR, and fibrinogen. Urinalysis includes analysis of protein, glucose, ketones specific, blood, specific gravity, pH, bilirubin, leukocytes, nitrite, urobilinogen urine red blood cells and urine while blood cells.
- Adverse events record

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- Patients will be dispensed and instructed to take the study drug QD daily from Day 1, in the morning before breakfast.

Investigators will explain to the patients the American Association for the Study of Liver Diseases guidance (Crabb et al, 2019) regarding diet and exercise. Investigators will collect the compliance to this guidance at each subsequent visit. Patients must make every effort to maintain the same diet/exercise treatment throughout the study. They will be asked about their compliance with this guidance at every visit. Answers will be documented in source documents and reported in the eCRF.

7.3. Study Site Visit (Day 7 – Week 1 ±2 days)

The following procedures or assessments will be performed:

- Concomitant medications record
- Partial physical examination
- Patient will be asked about any changes in alcohol consumption
- Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature. Temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study. Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording vital signs
- Pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale)
- Clinical laboratory assessments: biochemistry, hematology, urinalysis, and coagulation. Blood draws for clinical laboratory tests should be done predose. Biochemistry includes hemoglobin A1c, ALT, AST, ALP, GGT, LDH, creatine kinase, total and direct bilirubin, total protein, albumin, globulin, BUN, creatinine, eGFR, uric acid, amylase, sodium, potassium, calcium, magnesium, chloride, fasting glucose, TGs, TC, LDL-C, HDL-C, bile acids. Hematology includes complete blood cell count with differential (red blood cells, white blood cells, platelets, hemoglobin, and hematocrit). Coagulation includes PT, PTT, INR, and fibrinogen. Urinalysis includes analysis of protein, glucose, ketones specific, blood, specific gravity, pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine while blood cells.
- Wet biochemical NITs for NASH: procollagen C3,
- Adverse events record
- Patients will be instructed to take the study drug QD daily, in the morning before breakfast.

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7.4. Study Site Visit (Day 21 – Week 3 ±2 days)

The following procedures or assessments will be performed:

- Concomitant medications record
- Partial physical examination
- Alcohol Use Disorders Identification Test (AUDIT)
- Patient will be asked about any changes in alcohol consumption
- Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature. Temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study. Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording vital signs.
- Pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale)
- Clinical laboratory assessments: biochemistry, hematology, urinalysis, and coagulation. Blood draws for clinical laboratory tests should be done predose. Biochemistry includes hemoglobin A1c, ALT, AST, ALP, GGT, LDH, creatine kinase, total and direct bilirubin, total protein, albumin, globulin, BUN, creatinine, eGFR, uric acid, amylase, sodium, potassium, calcium, magnesium, chloride, fasting glucose, TGs, TC, LDL-C, HDL-C, bile acids. Hematology includes complete blood cell count with differential (red blood cells, white blood cells, platelets, hemoglobin, and hematocrit). Coagulation includes PT, PTT, INR, and fibrinogen. Urinalysis includes analysis of protein, glucose, ketones specific, blood, specific gravity, pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine while blood cells.
- Wet biochemical NITs for NASH: procollagen C3,
- Adverse events record
- Patients will be instructed to take the study drug QD daily, in the morning before breakfast.

7.5. Study Site Visit (Day 42 – Week 6 ±2 days)

On arrival at the study site on Day 42, the following procedures or assessments will be performed prior to dosing:

- Concomitant medications record

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- Alcohol Use Disorders Identification Test (AUDIT)
- Patient will be asked about any changes in alcohol consumption
- Wet biochemical NITs for NASH including: ALT, AST, ALP, platelet count, GGT, fasting glucose, hemoglobin A1c, TGs, TC, LDL-C, HDL-C, CK-18 (M65), procollagen C3, and HOMA index. Additional samples will be collected and stored for potential posthoc analysis of NIS-4.
- Imaging biomarkers NIT: MRI-PDFF
- Intense PK/PD assessments will be performed in subgroups (ie, n= from 30 to 40 patients). The sampling timepoints include predosing (0 hour up to 30 minutes before dosing) and postdosing 0.5 ± 3 minutes, 1 ±5 minutes, 1.5 ± 10 minutes, 2 ± 10 minutes, 3 ± 15 minutes, and 5 hours ± 15 minutes, which will be performed before lunch. Three collections PK/PD sampling will be performed in patients not participating in the PK/PD subgroup. The sampling timepoints will include predosing of 0 hour up to 30 minutes before dosing and postdosing of 1±0.5 hour and 4 hours ± 15 minutes, which will be performed before lunch. The predosing will be performed before the breakfast (low fat/sugar-diet breakfast), which will be arranged before 0.5-hour postdose.
- Partial physical examination
- Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature. Temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study. Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording vital signs
- Pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale)
- Clinical laboratory assessments: biochemistry, hematology, urinalysis, and coagulation. Blood draws for clinical laboratory tests should be done predose. Biochemistry includes LDH, creatine kinase, total and direct bilirubin, total protein, albumin, globulin, BUN, creatinine, eGFR, uric acid, amylase, sodium, potassium, calcium, magnesium, chloride, bile acids. Hematology includes complete blood cell count with differential (red blood cells, white blood cells, platelets, hemoglobin, and hematocrit). Coagulation includes PT, PTT, INR, and fibrinogen. Urinalysis includes analysis of protein, glucose, ketones specific, blood, specific gravity, pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine while blood cells.
- Adverse events record

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- Once dispensed, patients will be instructed to take the study drug QD daily, in the morning before breakfast.

7.6. Phone Call (Day 63 – Week 9 ±2 days)

At Week 9 patients will be contacted by phone call to provide information about:

- Concomitant medications record
- Patient will be asked about any changes in alcohol consumption
- Pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale)
- Adverse events record.
- Patients will be instructed by phone to take the study drug QD daily, in the morning before breakfast. The patient will be asked to not take their morning dose on the Day 84 of Week 12 until the visit and after the predose PK sample collection.

7.7. Study Site Visit (Day 84 – Week 12 ±2 days)

On arrival at the study site on Day 84, the following procedures or assessments will be performed prior to dosing:

- Concomitant medications record
- Alcohol Use Disorders Identification Test (AUDIT)
- Patient will be asked about any changes in alcohol consumption
- Urine pregnancy test
- Wet biochemical NITs for NASH including: ALT, AST, ALP, platelet count, GGT, fasting glucose, hemoglobin A1c, TGs, TC, LDL-C, HDL-C, CK-18 (M65), procollagen C3, and HOMA index. Additional samples will be collected and stored for potential post-hoc analysis of NIS-4.
- Imaging biomarkers NITs: MRI-PDFF and cT1
- Magnetic resonance elastography testing will be performed only in patients enrolled at a site with capacity to conduct MRE
- Pharmacokinetic and PD assessments will include predosing of 0 hour up to 30 minutes before dosing and postdosing of 1±0.5 hour and 4 hours ± 15 minutes, which will be performed before lunch. The predosing will be performed before the breakfast (low fat/sugar-diet breakfast), which will be arranged before 0.5-hour postdose.

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- Physical examination
- Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature. Temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study. Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording vital signs.
- Pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale)
- Clinical laboratory assessments: biochemistry, hematology, urinalysis, and coagulation. Blood draws for clinical laboratory tests should be done predose. Biochemistry includes LDH, creatine kinase, total and direct bilirubin, total protein, albumin, globulin, BUN, creatinine, eGFR, uric acid, amylase, sodium, potassium, calcium, magnesium, chloride, bile acids. Hematology includes complete blood cell count with differential (red blood cells, white blood cells, platelets, hemoglobin, and hematocrit). Coagulation includes PT, PTT, INR, and fibrinogen. Urinalysis includes analysis of protein, glucose, ketones specific, blood, specific gravity, pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine while blood cells.
- Adverse events record.
- The assigned bottles will be returned to the site and no further dosing will occur.

7.8. Follow-up/End of Study Visit (Day 112 – Week 16 ±2 days)

Patients will return to the study site on Day 112 and the following assessments will be performed:

- Concomitant medications record
- Patient will be asked about any changes in alcohol consumption
- Partial physical examination
- Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature. Temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study. Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording vital signs.
- Pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale)
- Clinical laboratory assessments: biochemistry, hematology, urinalysis, and coagulation. Blood draws for clinical laboratory tests should be done predose. Biochemistry includes hemoglobin A1c, ALT, AST, ALP, GGT, LDH, creatine kinase, total and direct bilirubin, total protein, albumin, globulin, BUN, creatinine, eGFR, uric acid, amylase, sodium, potassium, calcium, magnesium, chloride, fasting glucose, TGs, TC, LDL-C, HDL-C, bile acids. Hematology includes complete blood cell count with differential (red blood

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cells, white blood cells, platelets, hemoglobin, and hematocrit). Coagulation includes PT, PTT, INR, and fibrinogen. Urinalysis includes analysis of protein, glucose, ketones specific, blood, specific gravity, pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine white blood cells.

- Wet biochemical NITs for NASH: procollagen C3,
-

7.9. Safety and Tolerability Assessments

7.9.1. Adverse Events

Adverse event definitions and assignment of severity and causality are detailed in Appendix 1.

Adverse events will be elicited from the patient by the study site staff using a nonleading question such as “How are you feeling today?” or “Have you had any health concerns since your last visit?”.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue the study drug (see Section 4.3.2).

7.9.1.1. Adverse Events of Special Interest

Each patient’s safety will be closely monitored during the study.

Liver events (eg, suspected drug-induced liver injury or liver toxicity), will be included as AEs of special interest in this study.

7.9.2. Reporting Serious Adverse Events

All SAEs, occurring after first dose until follow-up (EOT) and whether or not attributable to the study drug, must be reported manually by completing and submitting a paper SAE form. The SAE must be reported to Labcorp Drug Development and sponsor within 24 hours of obtaining knowledge of the event. The SAE report should include all available information requested on the SAE Form. Initial reports of SAEs should never be left on telephone voicemails. Always complete a paper SAE form and email to Labcorp Drug Development Patient Safety Solutions (PSS) at SAEintake@labcorp.com and to sponsor at dengrong@cascadepharm.com.

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

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Labcorp Drug Development PSS will forward SAE queries requesting incomplete or missing information by email to the site. It is the investigator's responsibility to be diligent in providing this information back to Labcorp Drug Development PSS as soon as it is available.

7.9.3. Data Monitoring Committee

Safety data in addition to PK and PD data will undergo formal review by an independent DMC who will meet at least once and ad hoc as needed and will be responsible for the oversight of overall safety of the study. They will receive unblinded data but strictly firewalled (except for the unblinded DMC support staff who are also firewalled) and barred from sharing any information with anyone else including Labcorp and sponsor personnel and will make recommendations on continuation or discontinuation of the study and/or modifications to continue the study.

There will be a DMC Charter to govern how the DMC will operate and will include details regarding safety data that will be reviewed such as AEs, SAEs, as well as safety labs such as chemistry, hematology, urinalysis, thyroid, lipid, and liver.

In addition, the DMC and the sponsor will have a low threshold to call an ad hoc meeting if there is emerging AE or safety data that raises a potential concern. The DMC are explicitly required to meet if any of the potential stopping rule cases described in Section 4.4.1 occur.

The DMC will also review the data analysis of the primary efficacy endpoint, mean changes in LFC (measured by MRI-PDFF) from baseline to Week 12, patients treated with active doses compared to the change from baseline in patients treated with placebo. Furthermore, DMC will review the PK/PD analysis outcomes and provide a recommendation for the study.

7.9.4. Pregnancy

Although not considered an AE, it is the responsibility of the investigator or their designee to report any pregnancy in a patient or the patient's sexual partner that occurs during the study. All patients who become pregnant must immediately discontinue the study drug and be withdrawn from the study. The patient will be followed to completion/termination of the pregnancy. This information is important for both drug safety and public health concerns. If a patient is found to be pregnant after the study treatment was administered, the investigator should report this to the contract research organization (CRO) and sponsor immediately via SAEintake@labcorp.com and dengrong@cascadepharm.com and document the pregnancy on the Pregnancy Form. Follow the Pregnancy Form guidelines for the study.

The investigator must make every effort to follow the patient until completion of pregnancy. If the events during the pregnancy and/or outcome of pregnancy (ie, complications regarding mother/baby) meet the criteria for classification of an SAE, the investigator must follow the procedures for reporting SAEs. If the study has closed before the birth, then a paper SAE from must be completed and sent to SAEintake@labcorp.com as soon as possible post birth.

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7.10. Efficacy Assessments

Changes in clinical activity will be evaluated from baseline to Week 12 and will include the following assessments:

- The LFC as measured by MRI-PDFF mean changes
- The proportion of patients with ≥30% reduction LFC, and mean changes
- The ALT mean changes
- The proportion of patients having a ≥30% reduction in ALT levels
- Inflammatory and fibrosis biomarkers (ALP, AST, GGT, platelet count, CK-18), procollagen C3, and ELF (namely tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid)
- The proportion of patients with cT1 ≥880 ms at the baseline having a ≥80 ms (milliseconds) reduction in cT1 levels
- Metabolic biomarkers (fasting glucose, insulin, HOMA index, hemoglobin A1c, and bile acids)
- Standard lipid panel (TC, calculated LDL-C, HDL-C, and TG)
- Lipid profile (nuclear receptor and metabolism-altering mechanisms of action)
- Insulin sensitivity index (lipoprotein insulin resistance index based on 6 lipoprotein parameters)
- Lipoprotein particle concentration and size including LDL-P, and HDL-P
- GlycA and branched-chain amino acid concentrations
- Bile acids profile (total), and C4 (an intermediate in the synthesis of bile acids from cholesterol and a biomarker of hepatic CYP7A1 activity)

Potential posthoc analysis will also be done from baseline to Week 12 after the last dose of study intervention, namely NIS4 (NASHnext). Serum will be saved for potential posthoc analysis of NIS-4 changes.

7.11. Clinical Laboratory Evaluations

A central laboratory will be used for hematology, biochemistry, urinalysis, and coagulation markers of all specimens collected.

Details on the collections, shipment of samples, and reporting of results by the central laboratory will be provided to investigators in the laboratory manual. The investigator must review the

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laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF (see Section 7.9.1). The signed laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered abnormal and clinically significant during participation in the study should be repeated per standard practices until the values return to normal or baseline or are no longer considered clinically relevant by the investigator or sponsor's medical monitor (or designee). If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Assessments (see Appendix 5).

7.12. Vital Signs, Physical Examination, and Other Safety Evaluations

Vital signs should be assessed prior to blood draws and will include blood pressure, pulse rate, respiratory rate, and body temperature (oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study). Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording ECGs. Additional vital signs assessments can be performed per site investigator (or designee) discretion.

A complete or partial physical examination (depending on the visit) will be performed at screening and all subsequent visits.

The complete physical examination will include the examination of general appearance, height (only performed at screening), weight, BMI, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological, and, if medically indicated, other exams will be performed. The partial examination includes the examination of cardiac, pulmonary, abdomen (including liver palpation), and skin by either a qualified physician, nurse practitioner, or other staff members in close contact with the investigator.
Information for all physical examinations must be included in the source documentation at the study site. Abnormal findings on physical examination will be documented in the source documentation and eCRF. New or worsened clinically significant abnormalities should be reported as an AE. Avoid recording separate signs and symptoms and use medical diagnosis if at all possible.

7.12.1. 12-lead Electrocardiogram

Assessment of a single 12-lead ECG will be obtained as specified in the Schedule of Assessments (see Appendix 5) to determine heart rate and measure PR, QRS, QT, and QTcF intervals and should be assessed prior to blood draws.

The same person should perform each assessment whenever possible. Electrocardiograms must be performed only after patients have been resting in the supine or semi-recumbent position for at

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least 5 minutes. Prior to an ECG being performed, the ECG operator should check the tracing to ensure that it is of high quality. At screening, an ECG will be measured to test for eligibility for study inclusion. For patients whose ECG is abnormal at screening due to technical/mechanical faults, the examination should be repeated on Week 12.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the data suggest a more detailed assessment of ECGs is required. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Any clinically significant abnormalities should be reported as AEs or medical history on the eCRF.

7.13. Pharmacokinetic and Pharmacodynamic Analysis

7.13.1. Blood Sample Collection, Processing, and Analysis

Whole blood samples will be collected for measurements of the plasma concentration of CS0159 and PD biomarkers. The PK/PD blood samples will be collected as follows:

For intense PK/PD sampling:

- On Days 1 and 42 (Week 6) PK/PD analysis will be performed in subgroups containing from 30 to 40 patients. The sampling timepoints include predose (within 30 minutes before dosing) and 0.5 hour (±3 minutes), 1 hour (±5 minutes), 1.5 hours (±10 minutes), 2 hours (±10 minutes), 3 hours (±15 minutes), and 5 hours (±15 minutes) postdose before lunch.

- On Day 84 (Week 12) the sampling timepoints include predose (within 30 minutes before dosing) and 1 hour (±30 minutes), and 4 hours (± 15 minutes) postdose before lunch.

The predosing will be performed before the breakfast (low fat/sugar-diet breakfast), which will be arranged before 0.5 hour postdose.

Three collections PK/PD sampling will be performed in patients not participating in the PK/PD subgroup. Samples should be collected on Day 1, Day 42 (Week 6), and Day 84 (Week 12). The sampling timepoints will include predose of 0 hour (within 30 minutes before dosing) and postdose of 1 ±0.5 hour and 4 hours (±15 minutes).

The predosing will be performed before the breakfast (low fat/sugar-diet breakfast), which will be arranged before 0.5-hour postdose. The 4-hour postdosing timepoints will be performed before lunch.

Plasma PK sample analysis will be performed using validated procedures and methods at a central laboratory. PD biomarkers include serum C4 and plasma FGF19. The dosing for all PK/PD visits should be done on site.

Blood (4 mL) samples for PK/PD analysis will be obtained in vacuum blood collection tubes prior to dosing and at the timepoints delineated in the Schedule of Assessments (see Appendix 5).

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The actual collection time of each sample must be recorded in the source data and eCRF.

The sponsor will supply complete written instructions for collection, handling, processing, storage, and shipping of samples in the laboratory manual.

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8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of Sample Size

The sample size of 40 patients per active dose groups with 20 patients in placebo group would provide 80% statistical power under the following assumptions:

- $\alpha = 0.05$, 2-sided test
- Placebo mean % Δ from baseline in LCF = -10%, active mean % Δ from baseline in LCF = -25%
- Common standard deviation= 19%.

8.2. Analysis Populations

The following analysis populations will be included in this study:

- **Safety Analysis Set (SAS):** All randomized patients who receive at least 1 dose of the study drug or placebo. Patients will be analyzed according to the treatment received. The SAS will be the study population used for presentation of safety information.

- **Full Analysis Set (FAS):** All randomized patients who had at least one dose of study treatment. Patients will be analyzed according to their randomized treatment. The FAS will be the study population used for the presentation of efficacy analyses.

- **Pharmacokinetic Analysis Set:** All randomized patients who receive an active study drug and who have any measurable plasma concentration of CS0159 for analysis. Patients will be analyzed according to the treatment actually received. The PK Analysis Set will be the study population used for presentation of PK information.

8.3. General Considerations

Complete details of the statistical analyses, methods, and data conventions will be described in the SAP. Statistical analysis will be performed using SAS, version 9.4 or higher (SAS Institute, Inc., Cary, NC).

As a general rule, categorical data will be summarized using frequency and percentage, and continuous variables will be summarized using descriptive statistics (number of observations, mean, standard deviation, minimum, median, and maximum). The extent of missing data will be reported.

Summary data will be presented by treatment group and overall, and when applicable, by assessment time. Individual patient data will be listed by patient number, and, where applicable, by assessment time.

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8.4. Safety Analysis

Safety variables include incidence of AEs (or TEAEs), clinical laboratory assessments, vital signs, ECG results, and physical examination findings. All safety analyses will be based on the SAS population. Safety parameters will be listed and summarized using descriptive statistics, no formal statistical analysis of the safety data will be performed.

Summary data will be provided for all AEs by treatment group. The incidence of AEs, related AEs, SAEs, and AEs leading to discontinuation of the study treatment will be presented by Medical Dictionary for Regulatory Activities (version 25.0) system organ class (SOC) and preferred term. In addition, the incidence of AEs by severity will be presented by SOC and preferred term.

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

Laboratory test variables will be summarized by treatment group and visit using descriptive statistics (number of patients, mean, standard deviation, minimum, maximum, and mean change from baseline). Shift tables (low, normal, high) between baseline and postbaseline timepoints will be presented by laboratory test and treatment group. Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries but will be listed. Data obtained from laboratory tests not required by the protocol will not be summarized but will be listed.

Descriptive statistics of vital signs and ECG results at each visit will be presented by treatment group. Physical examination findings will be listed for each patient.

8.5. Efficacy Analysis

All efficacy endpoints will be evaluated on the FAS of patients. Details of statistical analysis are described in the SAP. Analyses based on statistical models will report the model results, such as LS mean difference between each study treatment and placebo groups along with the corresponding confidence interval and p-value. All hypothesis tests will be 2-sided at the 0.05 level of significance unless otherwise stated in the SAP.

8.5.1. Primary Efficacy Outcome Measures

Week 12 MRI-PDFF data for early terminations (patients who terminate prior to the scheduled Week 12 MRI-PDFF) will be imputed using the patient's early termination MRI-PDFF as well as available Week 12 data from other patients in the patient's randomized cohort. For patients with early termination due to drug-related TEAEs, Week 12 MRI-PDFF data will be imputed using that patient's early termination MRI-PDFF. Data will also be summarized with descriptive statistics and 95% confidence intervals.

Sensitivity analyses will be described in the SAP. The sensitivity analyses will be performed to

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evaluate the robustness of the primary efficacy results. The method to impute missing data will be determined once the pattern and extent of missing data are better understood.

8.5.2. Secondary Efficacy Outcome Measures

Secondary efficacy endpoints comparing proportions will be analyzed using the Cochran, Mantel, and Haenszel (CMH) method. Secondary endpoints comparing mean changes or other continuous variables will be analyzed in the same manner as the primary endpoint.

8.6. Pharmacokinetic Analysis

Plasma PK parameters of each dose level will be calculated from the concentrations of unchanged CS0159. Plasma concentrations and PK parameters will be summarized using descriptive statistics. Individual and mean CS0159 concentration-time profiles will also be presented graphically. Summary statistics will include mean (arithmetic and geometric), standard deviation, CV (arithmetic and geometric), median, minimum, and maximum.

Non-compartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin® (Version 8.1 or higher). Plasma concentrations of CS0159 and plasma PK parameters will be listed and summarized for each assessed visit and scheduled timepoint (if applicable) by treatment group for the PK Analysis Set.

Details of the analysis plan will be provided in the SAP.

8.7. Pharmacodynamic Analysis

Pharmacodynamics parameters of FGF19 and C4 will be listed and summarized as appropriate for CS0159 using descriptive statistics for the FAS.

The PK/PD relationship may be explored using a graphic approach and correlation coefficients as appropriate.

Details of the analysis plan will be provided in the SAP.

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10. APPENDICES

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Appendix 1 – Adverse Event Definitions

Definitions

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. This includes the following:

- Any clinically significant worsening of a pre-existing condition.
- Note: Emergence of a new pathogen associated with a clinical event during therapy at a site other than the initial site of infection will be considered an AE.
- Any recurrence of a pre-existing condition.
- An AE occurring from overdose of a sponsor study drug whether accidental or intentional (ie, a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a sponsor study drug (ie, use for nonclinical reasons).
- An AE that has been associated with the discontinuation of the use of a sponsor study drug.

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

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

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered treatment emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the follow-up visit.

Reporting of Adverse Events

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

Adverse event reporting begins from the time of first dose and ends 30 days after the last dose of study drug.

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Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- **Severe**: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- **Not Related**: When the AE is definitely caused by the patient's clinical state, or the study procedure/conditions.
- **Unlikely Related**: When the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: When the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Related**: When the AE follows a reasonable temporal sequence from administration of the drug, abates on discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Action Taken for Adverse Events

The investigator or designee will record the action taken for the AE in the electronic case report form. Actions taken will include:

- **Dose Not Changed**: The medication schedule was not changed.
- **Dose Reduced**: The medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
- **Drug Interrupted**: The medication schedule was modified by temporarily terminating the prescribed regimen of medication.

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- **Drug Withdrawn**: The medication schedule was modified through termination of the prescribed regimen of medication.
- **Not Applicable**
- **Unknown**

Follow-up of Adverse Events

Patients who discontinue from the study will be asked to complete final study procedures (Week 12 visit). All AEs and serious AEs (SAEs) that are ongoing at the time of discontinuation will be followed for 30 days, or until resolution, or until the investigator has determined that the AEs and SAEs have stabilized.

Adverse Drug Reactions

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

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

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

Serious Adverse Events

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

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

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such events include allergic bronchospasm requiring

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

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

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

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

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

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

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

Adverse Events of Special Interest

An AE of special interest (serious or nonserious) is 1 of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the study sponsor to other parties (eg, regulators) might also be warranted.

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Common Terminology Criteria for Adverse Event (CTCAE)

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **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)*.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- **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. A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for Grade selection.
- **Grade 5**: Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Reference:
Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017 Accessed on 21 July 2022.
www.efaidnbmnnnibpcajpcglclefindmkaj/https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

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Appendix 2 – Clinical Laboratory Evaluations

The following clinical laboratory analytes will be assessed:

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Biochemistry:	**Hematology:**
Albumin	Differential WBC Count (absolute): basophils, eosinophils, lymphocytes, monocytes, neutrophils
ALP	Hematocrit
ALT	Hemoglobin
Amino-terminal propeptide of type III procollagen	Platelet count
Amylase	Red blood cell count
AST	White blood cells count
Bile acids	Reticulocyte count
BUN	
Calcium	**Coagulation:**
Chloride	Fibrinogen
Creatine kinase	International normalized ratio
Creatinine	Partial thromboplastin time
Cytokeratin-18 (M65)	Prothrombin time
Direct bilirubin	
eGFR	**Pharmacodynamics biomarkers:**
Fasting glucose	7α-hydroxy-4-cholesten-3-one (C4)
GGT	Fibroblast growth factor 19 (FGF19)
Globulin	
Glucose	**For Women only:**
GlycA	Serum/urine beta-human chorionic gonadotropin pregnancy
HDL-C and HDL-P	
Hemoglobin A1c	**Rapid test for assessing infectious diseases:**
HOMA index	HAV IgM antibody
Hyaluronic acid	HBsAg
Insulin	HCV
Insulin sensitive index	HCVAb
LDH	HCV RNA quantification
LDL-C and LDL-P	HIV
Magnesium	
Metalloproteinases 1	**Urinalysis**
NIS-4	Protein
Potassium	Glucose
Procollagen C3	Ketones
Sodium	Blood
Total bilirubin	Specific gravity
Total cholesterol	pH
Triglycerides	Bilirubin
Uric acid	Leukocytes
	Urobilinogen
	Nitrite
	Urine red blood cells
	Urine while blood cells

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase;

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HAV = hepatitis A virus; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; HCVAb = hepatitis C virus antigen; HDL-C = high-density lipoprotein cholesterol; HDL-P: high-density lipoprotein particle; HIV = human immunodeficiency virus; HOMA = homeostatic model assessment for insulin resistance; Ig = immunoglobulin; LDH = lactate dehydrogenase; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle: RNA = ribonucleic acid

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Appendix 3 – Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) good clinical practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/ethics committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

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

The investigator will be responsible for the following:

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

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

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

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

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

Patient Data Protection

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

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

Disclosure

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

Data Quality Assurance

The following data quality steps will be implemented:

- All patient data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk

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management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in accordance with 21 CFR 312.62(c) (US site) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

- As per ICH GCP, the essential documents 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 requirements or by an agreement with the sponsor.

Investigator Documentation Responsibilities

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

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

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

Publications

If on completion of the study the data warrant publication, the investigator may publish the results in recognized (refereed) scientific journals patient to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process shall occur:

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

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Appendix 4 – Liver Safety Required Actions and Follow-up Assessments

Patients should be instructed to contact study personnel immediately if they notice any of the following signs and symptoms or have healthcare interactions outside of the study setting:

- Symptoms of liver impairment include yellowing of the skin or the whites of the eyes, pale-colored stools, and a change in urine color from pale to dark (amber) suggesting impaired bilirubin metabolism
- More general signs and symptoms of ascites and encephalopathy: e.g., confusion, swelling of the legs or abdomen
- Non-specific signs and symptoms of impaired health: e.g., nausea, vomiting, abdominal pain, diarrhea, weight loss, fever, chills, worsening or new fatigue, weakness, loss of appetite
- Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (e.g., severe abdominal pain, vomiting, and persistent diarrhea) and should be a prompt indication to interrupt the investigational product and complete a full evaluation of the patient.

Table 1: Algorithm for monitoring and interrupting study drug for hepatoxicity and hepatocellular DILI signals

Event	Action to Be Taken
In patients with BLM of ALT and AST <1.5 × ULN: If ALT or AST >3 × ULN or TBL >1.5 × BLM OR **In patients with BLM of ALT or AST >1.5 × ULN:** If AST or ALT>2 × BLM or TBL >1.5 × BLM	• Repeat testing of ALT, AST, ALP and TBL within 48−72 hours, with inquiry about symptoms. • If repeat testing above confirms initial result: o Repeat ALT, AST, ALP, and TBL two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the patient is asymptomatic. o Obtain a more detailed history of symptoms and prior or concurrent diseases. o Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

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	○ Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease. ○ Obtain a history of exposure to environmental chemical agents. ○ Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin). ○ Consider gastroenterology or hepatology consultations. ○ Consider liver biopsy.
In patients with BLM of ALT and AST <2 × ULN: If ALT or AST increases to >5 × BLM	Interrupt or discontinue the study drug
In patients with BLM of ALT and AST ≥2 × ULN but < 5 × ULN: If ALT or AST increases to >3 × BLM	Interrupt or discontinue the study drug
In patients with BLM of ALT and AST ≥5 × ULN: If ALT or AST increases to >2 × BLM	Interrupt or discontinue the study drug
In patients with BLM in normal range or ALT or AST <1.5 × ULN: If ALT or AST increases to >3 × ULN accompanied by: a concomitant increase in TBL to >2 × ULN OR the INR concomitantly increases by >0.2 in any patients with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Interrupt or discontinue the study drug
In patients with BLM of ALT or AST >1.5 × ULN: If ALT or AST increases to >2 × BLM accompanied by: a concomitant increase in TBL to >2 × BLM OR the INR concomitantly increases by >0.2 in any patients with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Interrupt or discontinue the study drug

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In all the above instances, continue monitoring the liver enzymes. If the levels of liver enzymes return to baseline levels, or alternate causes are clearly identified, resumption of dosing may be considered in some cases after discussion with the Medical Monitor.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BLM = baseline measurement; INR = International Normalized Ratio; NASH = nonalcoholic steatohepatitis; TBL = total bilirubin; ULN = upper limit of normal.

Liver biochemistry will be assessed to evaluate potential hepatic injury. These assessments will be performed at: a) each protocol-specified visit; b) unscheduled visits as needed in the event of signs or symptoms of suspected hepatic injury or if laboratory alerts have been triggered. It is a priority that laboratory assessments be completed as required and that the central laboratory be used for assessments whenever possible. In the event that a patient cannot complete a scheduled or unscheduled visit, or there is an event that triggers a need for an immediate assessment, the use of a local lab is permissible at the discretion of the investigator. In such cases, the investigator will obtain laboratory results as well as laboratory normal ranges.

The diagnostic approach to DILI can be tailored according to the pattern of liver injury at presentation. The R-value is defined as serum ALT/ULN divided by serum ALP/ULN. By common convention, R>5 is labeled as hepatocellular DILI, R<2 is labeled as cholestatic DILI, and 2<R<5 is labeled as mixed DILI. The pattern of liver injury provides a useful framework to allow one to focus on differential diagnosis and further evaluation. However, the same medication can present with varying laboratory profiles and clinical features in individual DILI patients.

In patients with suspected hepatocellular or mixed DILI and following the recent American College of Gastroenterology Guideline (Chalasani et al., 2021) for DILI:

- Acute viral hepatitis (A, B, and C) and autoimmune hepatitis should be excluded with standard serologies and HCV RNA testing.
- Anti-HEV IgM testing may be considered in selected patients where there is heightened clinical suspicion (e.g., recent travel in an endemic area, DILI phenotype is atypical, or there is no readily identifiable culprit agent). It should however be noted that the performance of the currently available commercial tests is not clear.
- It is recommended testing for acute cytomegalovirus, acute Epstein-Barr virus, or acute herpes simplex virus infection be undertaken if classical viral hepatitis has been excluded or clinical features such as atypical lymphocytosis and lymphadenopathy suggest such causes.
- It is recommended an evaluation for Wilson disease and Budd-Chiari syndrome when clinically appropriate.

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Typically, cholestatic DILI takes longer to resolve than the hepatocellular DILI. Some experts consider a less than 50% decline in the peak ALT value 30 days after stopping the suspected agent as reducing the likelihood of a DILI diagnosis. Others place the cutoff time for significant fall in ALT at 60 days. For cholestatic injury, the lack of a significant drop in AP or bilirubin (>50% drop in peak ULN or drop to<2 x ULN) at 180 days is considered significant.

In patients with suspected cholestatic DILI:

- Abdominal imaging (ultrasound, computed tomography scan, and MRI) will be performed in all instances to exclude biliary tract pathology and infiltrative processes
- Serological testing for PBC will be limited to those with no evidence of obvious biliary tract pathology on abdominal imaging
- Endoscopic retrograde cholangiography will be limited to instances where routine imaging including MRI or endoscopic ultrasound is unable to exclude impacted common bile duct stones, PSC, or pancreaticobiliary malignancy.

Table 2: Algorithm for monitoring and interrupting study drug for cholestatic DILI signals

Baseline[a]	Event[b]	Action[c]
TBL ≤ ULN	TBL ≥2x BLM and > ULN	Interrupt or discontinue the study drug
TBL > ULN	TBL ≥1.5x BLM or ≥ 3.0 mg/dL, whichever occurs first	Interrupt or discontinue the study drug
ALP ≤ ULN	ALP ≥2x BLM and >ULN	Interrupt or discontinue the study drug
ALP > ULN	ALP ≥2x BLM or ≥1000 U/L, whichever occurs first	Interrupt or discontinue the study drug

Abbreviations: ALP = alkaline phosphatase; TBL = total bilirubin; BLM = baseline measurement; ULN = upper limit of normal

[a] Baseline values for DILI monitoring for ALP and TBL should be determined based upon average of two tests between screening and Day 1. Adapted from Palmer et al., 2020.
[b] Liver signs and symptoms to include: new onset severe fatigue or significant worsening of baseline fatigue; new onset severe pruritus or significant worsening on baseline pruritus; nausea, vomiting, RUQ pain; fever, rash, or >5% eosinophilia; new onset of hepatic decompensation (e.g., ascites, variceal bleeding, hepatic encephalopathy)
[c.] Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. Patients who discontinue from the study will participate in the end of treatment visit at the time of discontinuation.

These recommendations are intended to be flexible and should be adjusted as deemed appropriate when applied to individual patients.

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References:

Chalasani, Naga P. MD, FACG1; Maddur, Haripriya MD2; Russo, Mark W. MD, MPH, FACG3; Wong, Robert J. MD, MS, FACG (GRADE Methodologist)4; Reddy, K. Rajender MD, FACG5, on behalf of the Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. The American Journal of Gastroenterology: May 2021 - Volume 116 - Issue 5 - p 878-898 doi: 10.14309/ajg.0000000000001259.

Palmer, M., Regev, A., Lindor, K., Avigan, M. I., Dimick-Santos, L., Treem, W., Marcinak, J. F., Lewis, J. H., Anania, F. A., Seekins, D., Shneider, B. L., & Chalasani, N. (2020). Consensus guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury occurring during clinical trials in adults with chronic cholestatic liver disease. *Alimentary pharmacology & therapeutics*, 51(1), 90–109.

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Appendix 5 – Schedule of Assessments

Table 3: Schedule of Assessments

Study Procedures	**Screening (Up to 2 Visits)**	**Treatment Period**						**Safety Follow-up Period**	
	Days -56 to -1 (8 weeks)	**Day 1**	**Week 1** (Day 7) ±2	**Week 3** (Day 21) ±2	**Week 6** (Day 42) ±2	**Week 9** (Day 63) ±2 Phone call	**Week 12** (Day 84) ±2 EOT	**Week 16** (Day 112) ±2	**Unscheduled Visit**[15]
Informed Consent	X								
Demographic Data	X								
Medical History	X								
Prior and Concomitant Medications[1]	X	X	X	X	X	X	X	X	X
Inclusion/ Exclusion	X	X							
Hepatitis A virus (anti-HAV), Hepatitis B surface antigen (HBsAg), Hepatitis C virus (anti-HCV), and anti-HIV test	X								
Serum/Urine Pregnancy Test[2]	X	X					X		
AUDIT	X	X		X	X		X		
Changes in alcohol consumption		X	X	X	X	X	X	X	X
Wet Biochemical NITs for NASH[3]		X	X	X	X		X	X	

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MRI-PDFF	X				X		X		
Study Procedures	**Screening (Up to 2 Visits)**	**Treatment Period**						**Safety Follow-Up Period**	
	Days -56 to -1 (8 weeks)	**Day 1**	**Week 1** (Day 7) ±2	**Week 3** (Day 21) ±2	**Week 6** (Day 42) ±2	**Week 9** (Day 63) ±2 Phone call	**Week 12** (Day 84) ±2 EOT	**Week 16** (Day 112) ±2	**Unscheduled Visit**[15]
cT1[4]	X						X		
MRE[5]	X						X		
PK/PD Assessments[6]		X			X		X		
IWRS Randomization		X							
Physical Examination	X	X					X		X
Partial Physical Examination[7]			X	X	X			X	X
12-lead ECG[8]	X								X
Vital Signs[9]	X	X	X	X	X		X	X	X
Pruritus Assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale [10])		X	X	X	X	X	X	X	X
Clinical Laboratory Assessments[11]: Biochemistry, Hematology, Urinalysis[12], and Coagulation[13]	X	X	X	X	X		X	X	X
AEs		X	X	X	X	X	X	X	X
CS0159 or Placebo Administration[14]		X	X	X	X	X	X		

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Abbreviations: AE = adverse event; AUDIT = alcohol use disorders identification test; cT1 = correct T1; ECG = electrocardiogram; EOT = end of treatment; HAV = hepatitis A virus; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgM = immunoglobulin; IWRS = interactive web response system; PD = pharmacodynamic; PK = pharmacokinetic; NASH = nonalcoholic steatosis hepatic; NIT = noninvasive testing; MRE = magnetic resonance elastography; MRI-PDFF = magnetic resonance imaging proton density fat fraction.

[1] Any NASH-related medication taken within 6 months prior to first screening visit and all other ongoing medications at signing of the ICF should be recorded in the source documents and eCRF (see concomitant medication rules in exclusion criterion #26).

[2] Female patients of childbearing potential (<2 years after menopause and not permanently sterile) must have a serum beta-human chorionic gonadotropin pregnancy test at screening and must have a urine beta-human chorionic gonadotropin pregnancy test within 24 hours before the first dose of study intervention. At Day 84 female patients must have a urine pregnancy test.

[3] Wet biomarkers: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), platelet count, gamma-glutamyl transferase (GGT), fasting glucose, hemoglobin A1c, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), cytokeratin-18 (M65), procollagen C3, insulin and homeostatic model assessment for insulin resistance index. (Additional samples will be collected and stored for potential post-hoc analysis of NIS-4). On Week 1, 3 and 16, only the procollagen C3 will be collected.

[4] Correct T1 testing applies only to those patients who meet inclusion criteria and will be enrolled in this study.

[5] Magnetic resonance elastography testing applies only to those sites with the capacity to conduct MRE for those patients who meet inclusion criteria and will be enrolled in this study.

[6] Intense PK/PD assessments on Day 1 and Day 42 (Week 6) will be performed in subgroups (ie, n= from 30 to 40 patients). The sampling timepoints include predosing (0 hour) and postdosing 0.5, 1, 1.5, 2, 3, and 5 hours, which will be performed before lunch. On Day 84 (Week 12), the sampling timepoints will include predosing of 0 hour and postdosing of 1±0.5 hour and 4 hours, which will be performed before lunch. The pre-dosing will be performed before the breakfast (low fat/sugar-diet breakfast), which will be arranged before 0.5-hour post-dose. Three collections PK/PD sampling will be performed in patients not participating in the PK/PD subgroup. Samples will be collected on Day 1, Day 42 (Week 6) and Day 84 (Week 12). The sampling timepoints will include pre-dosing of 0 hour and post-dosing of 1±0.5 hour and 4 hours. The pre-dosing will be performed before the breakfast (low fat/sugar-diet breakfast), which will be arranged before 0.5-hour post-dose. The 4-hour postdosing timepoints will be performed before lunch. PD biomarkers include serum 7α-hydroxy-4-cholesten-3-one and plasma fibroblast growth factor 19. The dosing for all PK/PD visits should be done on site.

[7] Examine Cardiac, Pulmonary, Abdomen (including Liver palpation), and Skin by either a qualified physician, nurse practitioner, or other staff members in close contact with the investigator.

[8] Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording ECGs. The ECGs should be assessed prior to blood draws. To be repeated on Week 12 in case some abnormality is observed.

[9] Vital signs include blood pressure, pulse rate, respiratory rate, and body temperature. Body temperature by oral, axillary, or tympanic route may be permitted provided the same route is used for the patient throughout the study. Patients should be rested in a supine or semi-recumbent position for ≥5 minutes before recording vital signs. The vital signs should be assessed prior to blood draws.

[10] For Week 9 will be assessed the possibility of covering pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale) over a phone call and/or digital platforms.

[11] Blood draws for clinical laboratory tests should be done predose in all study visits (as applicable).

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[12] Urinalysis includes analysis of protein, glucose, ketones specific, blood, specific gravity, pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine while blood cells.
[13] Biochemistry includes hemoglobin A1c, ALT, AST, ALP, GGT, lactate dehydrogenase, creatine kinase, insulin, total and direct bilirubin, total protein, albumin, globulin, blood urea nitrogen, creatinine, estimated glomerular filtration rate, uric acid, amylase, sodium, potassium, calcium, magnesium, chloride, fasting glucose, triglycerides, total cholesterol, LDL-C, HDL-C, bile acids. Hematology includes complete blood cell count with differential (red blood cells, white blood cells, platelets, hemoglobin, and hematocrit), differential white blood cells count absolute (basophils, eosinophils, lymphocytes, monocytes and neutrophils) and reticulocyte count. Coagulation includes prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen.

[14] Remind patients about the daily study intervention administration on Days 1, 7, 21, 42, and 63. And dispense and/or return investigational product only on Days 1, 42, and 84.

[15] For unscheduled visits, assessments not marked in the SoA may be performed at the discretion of the Investigator. Investigators will do any test if they think it is necessary rather than marked in the SOA, however, AE assessments must be completed at a minimum unless the unscheduled visit is during the screening. The unscheduled visits are of limited significance, all unscheduled visits and all tests are based on the Investigators' judgment.

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Appendix 6 – Protocol Amendment History

Amendment 1, 18 October 2022

Section # and Name	Description of Change	Brief Rationale
General	Dose scheme changed from 2 mg to 1.4 mg and from 4 mg to 2 mg	After new analysis on pop-PK, PK-PD, and safety data of MAD 1, 2, and 4 mg it has been decided that 1.4mg and 2.0 mg is the best dose scheme for this study
Synopsis Section 4.1 Inclusion Criteria #3	The biopsy-proven NASH was defined per the NASH Clinical Research Network (NASH CRN) Histologic Scoring System as NAFLD activity score (NAS) ≥4 (with ≥1 point in each component of steatosis, lobular inflammation, and hepatocellular ballooning) AND stage 1, 2, or 3 fibrosis	Updated definition of the biopsy-proven NASH
Section 1 Introduction	All dose levels of MAD (0.4 mg, 1 mg, 2 mg, and 4 mg) have already been completed.	Phase I study updated data
Section 3.4 Selection of Doses in the Study	Safety margin to the human exposure of CS0159 updated from >1.6 x to >3.3	PK and PD data were updated to justify the selection of doses
Section 5.2 Preparation, Storage, Handling and Accountability	Patients (independently of the group) will receive 2 bottles with CS0159 or placebo tablets with enough tablets to cover 6 weeks plus 18 days	Updated information about the pre-packaged dose kits according to the new dose scheme

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Amendment 2, 27 October 2022

Overall Rationale for the Amendment 2:

The overall rationale (one primary driver) for the changes implemented in the protocol amendment 2 is the updated data from the Phase I study.

Section # and Name	Description of Change	Brief Rationale
Section 3.4 Selection of Doses in the Study	Safety margin to the human exposure of CS0159 updated from >3.3 x to >3.6. Updated $AUC_{0-\infty}$, $t_{1/2}$ and t_{max} data.	More PK and PD data were updated to justify the selection of doses

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Amendment 3, 05 December 2022

Overall Rationale for the Amendment 3:

The primary purpose of this amendment was to address comments received from the FDA during the protocol version 3.0 review and to include the following urinalysis: pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine white blood cells. In addition, minor text clarifications were made. Changes incorporated in this amendment are described in the following table.

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Section # and Name	Description of Change	Brief Rationale
Synopsis and Section 8.2 Analysis Population	Revised the Full Analysis Set definition.	For clarification: changes are closely tied to the primary objective and sample size calculation.
Section 4.3 Discontinuation Criteria	Added new subsection **4.3.3 Individual Discontinuation Criteria**	To align with the FDA request during protocol version 3.0 review
Section 4.3.3.1 Liver Injury	Revised criteria of liver injury	To align with the FDA request during protocol version 3.0 review
Section 4.4 Study Termination	Added new subsection **4.4.1 Study Stopping Rules**	To align with the FDA request during protocol version 3.0 review
Section 7 Study Assessments and Procedures (Subsections 7.2, 7.5 and 7.7)	Added window period for PK collection	For clarification
Section 7 Study Assessments and Procedures (Subsection 7.9.2)	Revised text about the reporting of SAEs	For clarification

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Section 7 Study Assessments and Procedures (Subsection 7.9.3)	Revised text about the need DMC to meet if any of the potential stopping rule cases described in new Section 4.4.1 occur.	For clarification
Section 7 Study Assessments and Procedures (Subsection 7.12)	Height measurement (only performed at screening) and BMI added to the complete physical examination	For clarification
Section 8.6 Pharmacokinetic Analysis	Revised text	For clarification
Appendix 2 Clinical Laboratory Evaluations	Added total bilirubin	Table updated to add new biochemistry
Appendix 2 Clinical Laboratory Evaluations, Appendix 5 Schedule of Assessments and Section 7 Study Assessments and Procedures (Subsections 7.1, 7.2, 7.3, 7.4, 7.5, 7.7 and 7.8	Added urinalysis with following parameters: pH, bilirubin, leukocytes, nitrite, urobilinogen, urine red blood cells and urine white blood cells	Normal safety testing
Appendix 4 Liver Safety Required Actions and Follow-up Assessments	Revised Appendix 4 content to emphasize the monitor of cholestatic drug-induced liver injury (DILI)	To align with the FDA request during protocol version 3.0 review: closely monitor the cholestatic DILI including serum ALP, TBL, ALT and AST

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Appendix 5 Schedule of Assessments	Revised footnote #11	For clarification

Amendment 4, 20 February 2023

Overall Rationale for the Amendment 4:

The primary purpose of this amendment was to address comments received from the FDA during the protocol version 4.0 review to include routine monitoring of patient's alcohol consumption and the following exclusion criteria:

- Patients with a history or diagnosis of:
    - Solid organ transplantation and hematopoietic transplantation
    - Multiple endocrine neoplasia (MEN I or MEN II)
- Administrative corrections with discrepancies between the synopsis and main body of the protocol within the Exclusion criteria
- Administrative changes Interim Analysis to Data analysis.
- Including a stable dose of GLP1a for diabetes mellitus ≥ 6 months before screening.

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Section # and Name	Description of Change	Brief Rationale
Section 4.2 Exclusion criteria and Synopsis	Added the exclusion criterion Exclude subjects with a history or diagnosis of: a) Solid organ transplantation and hematopoietic transplantation b) Multiple endocrine neoplasia (MEN I or MEN II)	To align with FDA request during protocol version 4.0 review
Section 4.2 Exclusion criteria and Synopsis	Concomitant medications: subject not on a stable dose of GLP1a for diabetes mellitus ≥ 6 months before screening.	For clarity
Section 4.2 Exclusion criteria	Updating time restrictions on weight loss medication use prior to initiation of the study from 12 weeks to 6 months.	
Section 4.2 Exclusion criteria	History of acute liver complications due to gallstones (eg, acute cholecystitis or acute biliary obstruction) unless the patient has had a cholecystectomy (more than 3 months prior to screening).	For clarity
Synopsis and Sections 3.1 overall study design and 7 Study Assessments and Procedures	Revised text regarding timing of assessments for clinical laboratory and ECGs	For clarity

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Section 7 Study Assessments and Procedures (Subsections 7.2 through 7.8)	Added collection of change in alcohol consumption from patient	To align with the FDA request during protocol version 4.0 review
Section 7.9.3 Data Monitoring Committee	Revised text regarding review of data to update from the word interim to data analysis at week 12.	For clarity
Synopsis and Section 8.2 analysis populations	Revised text regarding definition of Full Analysis Set	To align with FDA requests during protocol version 4.0 review
Section 8.6 Pharmacokinetic Analysis	Revise text regarding description of analysis method	For clarity
Appendix 5 Schedule of Assessments	Added routine monitoring for changes in alcohol consumption and AUDIT	To align with FDA requests during protocol version 4.0 review