CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study Evaluating the Safety and Efficacy of Semaglutide, and the Fixed-Dose Combination of Cilofexor and Firsocostat, Alone and in Combination, in Subjects With Compensated Cirrhosis (F4) due to Nonalcoholic Steatohepatitis (NASH)
Study Acronym:	WAYFIND
Plain Language Short Title	Study of Semaglutide, and Cilofexor/Firsocostat, Alone and in Combination, in Adults With Cirrhosis Due to Nonalcoholic Steatohepatitis (NASH)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EU CT Number:** **ClinicalTrials.gov Identifier:**	155550 2021-001445-12 NCT04971785
Indication:	Nonalcoholic steatohepatitis (NASH)
Protocol ID:	GS-US-454-6075
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 2: 26 October 2023
Amendment History:	Original: 17 March 2021 Amendment 1: 25 June 2021 Amendment 2: 26 October 2023 High-level summaries of the history(ies) of amendment(s) are provided in Appendix 11.10.

Country-specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 11.9.

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study Evaluating the Safety and Efficacy of Semaglutide, and the Fixed-Dose Combination of Cilofexor and Firsocostat, Alone and in Combination, in Subjects With Compensated Cirrhosis (F4) due to Nonalcoholic Steatohepatitis (NASH)
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Regulatory Agency Identifier Numbers:	
IND Number:	155550
EU CT Number:	2021-001445-12
ClinicalTrials.gov Identifier:	NCT04971785
Study Sites Planned:	Approximately 250 sites globally
Objectives:	The primary objective of this study is as follows: • To evaluate whether the combination of semaglutide (SEMA) with the fixed-dose combination (FDC) of cilofexor (CILO; GS-9674) and firsocostat (FIR; GS-0976), hereafter referred to as CILO/FIR, causes fibrosis improvement (according to the NASH Clinical Research Network [CRN] classification) without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation) in participants with compensated cirrhosis due to NASH, as compared with placebo

The secondary objectives of this study are as follows:

- To confirm the contribution of CILO/FIR to fibrosis improvement without worsening of NASH in participants treated with the combination of SEMA and CILO/FIR by comparing with participants treated with SEMA alone
- To evaluate whether the combination of SEMA with the FDC of CILO/FIR causes NASH resolution (defined as lobular inflammation of 0 or 1 and hepatocellular ballooning of 0) in participants with compensated cirrhosis due to NASH, as compared with placebo
- To confirm the contribution of SEMA to NASH resolution in participants treated with the combination of SEMA and CILO/FIR by comparing with participants treated with CILO/FIR alone

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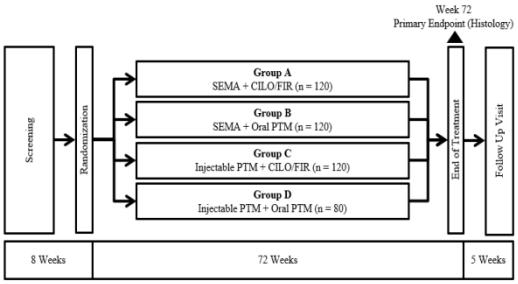
Study Design:

This is a Phase 2, randomized, double-blind, double-dummy, placebo-controlled study evaluating the efficacy and safety of SEMA, CILO/FIR, and their combination in participants with compensated cirrhosis due to NASH.

Participants meeting the study's entry criteria will be randomly assigned in a 3:3:3:2 ratio to 1 of 3 active treatment groups (SEMA + CILO/FIR, SEMA alone, CILO/FIR alone) or placebo-to-match (PTM), as shown in the figure below. Randomization will be stratified by the presence or absence of type 2 diabetes as determined by medical history or based on screening laboratory values if previously undiagnosed (ie, hemoglobin A_{1c} [HbA_{1c}] ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dL, confirmed on repeat testing), and by ELF score (≥ 11.30 or < 11.30 during screening).



CILO = cilofexor (GS-9674); firsocostat = FIR (GS-0976); PTM = placebo-to-match; SEMA = semaglutide

Number of Participants Planned:	Approximately 440 participants
Study Population:	Men and nonpregnant, nonlactating women between 18 and 80 years of age, inclusive, with compensated cirrhosis due to NASH, as determined by liver biopsy.
Duration of Treatment/ Intervention:	Participants will be treated for 72 weeks. Total study duration will be 85 weeks, including an 8-week screening period, a 72-week treatment period, and a 5-week follow-up period.
Diagnosis and Main Eligibility Criteria:	Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for the study. Inclusion Criteria: 1) Men and women between 18 and 80 years of age, inclusive, based on the date of the screening visit 2) Willing and able to give informed consent prior to any study-specific procedures being performed 3) Cirrhosis (F4) due to NASH as defined by 1 of the following: a) A historical liver biopsy within 180 days of screening that, in the opinion of the central pathologists, is evaluable and consistent with cirrhosis (F4) and NASH (defined as the presence of steatosis Grade ≥ 1, hepatocellular ballooning Grade ≥ 1, and lobular inflammation Grade ≥ 1, according to NAS) OR b) In participants without a qualifying historical liver biopsy, if FibroScan ≥ 9.9 kPa at screening, a screening liver biopsy may be performed. The screening liver biopsy must, in the opinion of the central pathologists, be evaluable and meet histologic criteria as specified in inclusion criterion 3a) OR c) In participants with a historical liver biopsy completed more than 180 days prior to screening that is consistent with cirrhosis (F4) and NASH, as determined by a local reader, a screening liver biopsy may be performed. The screening liver biopsy must, in the opinion of the central pathologists, be evaluable and meet histologic criteria as specified in inclusion criterion 3a)

4) The following laboratory parameters at screening, as determined by the central laboratory:

   a) Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m^2, as calculated by the Modification of Diet in Renal Disease (MDRD) equation to estimate creatinine clearance (CL_{cr})

   b) HbA_{1c} ≤ 10% (or reflex serum fructosamine ≤ 400 µmol/L if HbA_{1c} result is not quantifiable)

   c) Hemoglobin > 10.6 g/dL

   d) International normalized ratio ≤ 1.4, unless due to therapeutic anticoagulation

   e) Total bilirubin ≤ 1.3 × upper limit of normal (ULN) (unless due to an alternative etiology such as Gilbert's syndrome or hemolytic anemia)

   f) Serum albumin ≥ 3.5 g/dL

   g) Serum alkaline phosphatase (ALP) ≤ 2 × ULN

   h) Platelet count ≥ 125,000/µL

   i) Serum triglyceride level ≤ 250 mg/dL. If initial screening value is > 250 mg/dL, triglycerides may be retested during the screening period. Fasting serum triglycerides must be confirmed to be ≤ 250 mg/dL prior to Day 1. Management of hypertriglyceridemia may be initiated or modified at investigator discretion during the screening period

   j) ALT < 5 × ULN

5) Body mass index ≥ 23 kg/m^2 at screening

Exclusion Criteria:

1) Any history of decompensated liver disease in the opinion of the investigator, including clinically relevant ascites, hepatic encephalopathy (HE), or variceal bleeding

2) Child-Pugh (CP) score > 6 at screening, unless due to an alternative etiology such as Gilbert's syndrome or therapeutic anticoagulation

3) Model for End-Stage Liver Disease (MELD) score > 12 at screening, unless due to an alternative etiology such as therapeutic anticoagulation

4) Chronic hepatitis B virus infection (hepatitis B surface antigen positive)
5) Chronic hepatitis C virus (HCV) infection (HCV antibody and HCV RNA positive). Participants cured of HCV infection less than 2 years prior to the screening visit are not eligible
6) Other causes of liver disease based on medical history and/or central pathologists review of liver histology, including but not limited to: alcoholic liver disease, autoimmune disorders (eg, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis), drug-induced hepatotoxicity, Wilson disease, clinically significant iron overload, or alpha-1-antitrypsin deficiency
7) History of liver transplantation
8) Current or prior history of hepatocellular carcinoma (HCC)
9) HIV infection
10) Weight loss > 10% within 180 days of screening, or > 5% between the date of the biopsy used for eligibility and the date of screening
11) Any weight reduction surgery or procedure in the 2 years prior to screening or malabsorptive weight loss surgery (eg, Roux-en-Y or distal gastric bypass) at any time prior to screening
12) History of intestinal resection that could result in malabsorption of study drug
13) Planned coronary, carotid, or peripheral artery intervention or unstable cardiovascular disease in the opinion of the investigator, including any of the following:
    a) Unstable angina, myocardial infarction, coronary artery bypass graft surgery, or coronary angioplasty within 180 days prior to screening
    b) Transient ischemic attack or cerebrovascular accident within 180 days prior to screening
    c) Symptomatic valvular heart disease or hypertrophic cardiomyopathy
    d) Symptomatic congestive heart failure
    e) Uncontrolled or recurrent ventricular tachycardia or arrhythmia requiring an automatic implantable cardioverter defibrillator. Stable, controlled atrial fibrillation is allowed

f) An emergency room visit or hospitalization for confirmed cardiovascular disease within 180 days prior to screening

14) History of uncontrolled chronic pulmonary disease in the opinion of the investigator (eg, chronic obstructive pulmonary disease, interstitial lung disease) within 180 days prior to screening

15) Men who habitually drink greater than 21 units/week of alcohol or women who habitually drink greater than 14 units/week of alcohol (1 unit is equivalent to 12 oz/360 mL of beer, a 4 oz/120 mL glass of wine, or 1 oz/30 mL of hard liquor)

16) Positive urine drug screen for amphetamines, cocaine, or opiates (eg, heroin, morphine) at screening, unless due to a prescription medication (eg, oxycodone, methylphenidate) and the prescription and diagnosis are reviewed and approved by the investigator. Participants on stable methadone or buprenorphine maintenance treatment for at least 180 days prior to screening may be included in the study

17) Use of any prohibited concomitant medication prior to enrollment as described in Table 4:

a) Participants on vitamin E regimen ≥ 800 IU/day, or pioglitazone, must be on a stable dose in the opinion of the investigator for at least 180 days prior to the historical or screening liver biopsy

b) Participants taking antidiabetic medications must be on a stable dose, in the opinion of the investigator, for at least 90 days prior to the historical or screening liver biopsy

18) Participation in another investigational study of a drug or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to the date of screening and through the end of the study. Participation in a study of an investigational device may be approved by the medical monitor or designee

19) History of malignancy within 5 years of screening with the following exceptions:

a) Adequately treated carcinoma in situ of the cervix

b) Adequately treated basal or squamous cell cancer or other localized nonmelanoma skin cancer

20) For participants with type 2 diabetes diagnosed prior to the date of the screening visit OR based on screening visit HbA_{1c} ≥ 6.5%, participants must have no evidence of uncontrolled and potentially unstable retinopathy or maculopathy as

	determined by a fundoscopic examination performed starting 90 days prior to screening visit date through Day 1. If there has been worsening of the participant's visual function since a historical fundoscopic examination in the opinion of the investigator, then the fundoscopic examination must be repeated prior to Day 1 for eligibility. Pharmacological pupil dilation is a requirement unless using a digital fundus photography camera specified for nondilated examination
	21) Acute pancreatitis within 180 days prior to screening
	22) History or presence of chronic pancreatitis
	23) History of symptomatic gallbladder or biliary tract disease in the opinion of the investigator within 6 months prior to screening, unless a cholecystectomy has been performed
	24) Presence or history of type 1 diabetes
	25) Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullar thyroid carcinoma
	26) Treatment with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) in the period from 90 days prior to the screening visit and from 90 days prior to the date of the historical qualifying liver biopsy (if applicable)
	27) Female who is pregnant, breastfeeding, intends to become pregnant, or is of childbearing potential and not using an adequate contraceptive method
	28) Men who engage in heterosexual intercourse not using an adequate method of contraception
	29) Presence of any laboratory abnormality or condition that, in the opinion of the investigator, could interfere with or compromise a participant's treatment, assessment, or compliance with the protocol and/or study procedures. This includes a history of substance abuse and/or psychiatric condition requiring hospitalization and/or emergency room visit within 2 years of screening
	30) Known hypersensitivity to the study drug(s), metabolites, or formulation excipient(s)
	31) For participants who have not completed a series of an authorized COVID-19 vaccination regimen prior to screening, a positive result for COVID-19 on SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test

Study Procedures/ Frequency:	After signing the informed consent form (ICF), participants will complete a screening visit which will include the following assessments: complete medical history, complete physical examination (PE), vital signs, measurement of hip and waist circumference, assessment of ascites and HE, lifestyle counseling, calculation of the CP and MELD scores, laboratory assessments and biomarker sample collection, SARS-CoV-2 RT-PCR test (if necessary), serum pregnancy test (for women of child-bearing potential), urine drug screen, liver biopsy (if necessary), liver stiffness measured using FibroScan, abdominal ultrasound for evaluation of presence of HCC, gallstones, or other hepatobiliary disease (if applicable), standard 12-lead electrocardiogram (ECG), fundoscopic examination (if applicable), stool sample collection kit for Day 1 visit, and review of adverse events (AEs) and concomitant medications. Eligible participants will be randomly assigned on Day 1 in a 3:3:3:2 ratio to 1 of 3 active treatment groups or placebo: Group A: SEMA+CILO/FIR Group B: SEMA+PTM CILO/FIR Group C: PTM SEMA+CILO/FIR Group D: PTM SEMA+PTM CILO/FIR Prior to initial dosing, the following Day 1 assessments will be performed: symptom-driven PE, vital signs, measurement of hip and waist circumference, assessment of ascites and HE, lifestyle counseling, calculation of the CP and MELD scores, laboratory assessments and biomarker sample collection, urine pregnancy test (for women of child-bearing potential), PROs, and review of AEs and concomitant medications. After the screening period and randomization at Day 1, study visits will occur at Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72 or an early termination (ET) visit for those who discontinue from the study early, and a follow-up visit 5 weeks after the Week 72 or ET visit. At minimum, review of AEs and concomitant medications and safety laboratory tests will be performed at every visit.

While on the study, participants will undergo the following procedures and laboratory assessments:

- Vital signs and body weight at each visit
- Symptom-driven PE at each visit
- Assessment of ascites and HE at each visit
- Hip and waist circumference at Weeks 24, 48, and 72
- Lifestyle counseling at each visit
- FibroScan at Weeks 24, 48, and 72
- ELF test at Weeks 12, 24, 48, and 72
- Chemistry panel, hematology panel, lipid panel, coagulation and eGFR by MDRD at each visit
- HbA_{1c} and glycemic panel at Weeks 12, 24, 48, and 72
- Urine pregnancy test (for women of childbearing potential) every 4 weeks
- Blood and urine for biomarkers at Weeks 24, 48, and 72
- Stool for biomarkers at Weeks 48 and 72
- PROs at Weeks 24, 48, and 72
- Single PK blood sample at Week 4 (15 minutes to 3 hours postdose), Week 24 (anytime postdose), Week 48 (predose), Week 60 (15 minutes to 3 hours postdose), Week 72 (predose), and the ET visit (anytime). For PK sampling at Weeks 4, 48, 60, and 72, participants should be reminded not to take their oral study drug until advised to do so at their clinic visit
- 12-lead ECG at Week 72
- Liver biopsy at Week 72
- Abdominal ultrasound at Weeks 24, 48, and 72
- Fundus examination (participants with type 2 diabetes only) at Weeks 48 and 72, or ET visit (at discretion of investigator)

Participants who prematurely discontinue study drug are encouraged to return for an unscheduled visit at the discretion of the investigator or request of the medical monitor or designee for a safety evaluation. Participants should be encouraged to complete their remaining study visits in accordance with the Study Procedures Table if appropriate.

	Participants prematurely discontinuing from the study should complete an ET visit. At the ET visit, participants will undergo symptom-driven PE, vital signs, measurement of hip and waist circumference, assessments of ascites and HE, lifestyle counseling, calculation of the CP and MELD scores, laboratory tests, PK blood sample collection (anytime), pregnancy test (for women of childbearing potential), CCI [redacted], and review of concomitant medications and AEs. The following assessments should be performed unless completed within 12 weeks of the ET visit: abdominal ultrasound and FibroScan. The following assessments will be performed at the discretion of the investigator: PROs, ECG, fundus examination, biomarker sample collection (including blood and urine), and liver biopsy. All participants will have a follow-up visit 5 weeks after the Week 72 or ET visit. At the follow-up visit, participants will undergo a symptom-driven PE, vital signs, measurement of hip and waist circumference, assessment of ascites and HE, lifestyle counseling, calculation of the CP and MELD scores, laboratory tests, blood and urine collection for biomarkers, pregnancy test (for women of childbearing potential), and review of concomitant medications and AEs.
Test Product, Dose, and Mode of Administration:	SEMA 3.0 mg/mL solution for injection administered subcutaneously (SC) at a once-weekly dose from 0.24 mg to 2.4 mg (dose escalation over 16 weeks) using the 3.0 mL PDS290 prefilled pen injector CILO/FIR 30 mg/20 mg FDC tablet containing 30 mg (free-form equivalent) CILO and 20 mg FIR administered orally once daily with or without food
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-match SEMA 3.0 mg/mL solution for injection administered SC at a once-weekly dose from 0.24 mg to 2.4 mg (dose escalation over 16 weeks) using the 3.0 mL PDS290 prefilled pen injector Placebo-to-match CILO/FIR 30 mg/20 mg FDC tablet administered orally once daily with or without food

Criteria for Evaluation:

Safety:	The safety of study drug in participants with cirrhosis due to NASH will be assessed during the study through the assessment of vital signs, clinical laboratory tests, AEs, and concomitant medication usage. An external data monitoring committee (DMC) that consists of 2 hepatologists and a statistician will review the progress of the study. The DMC will convene after at least 55 participants have completed the Week 4 visit and approximately every 6 months thereafter to monitor the study for safety events.
Efficacy:	Primary endpoint: • ≥ 1-stage improvement in fibrosis (according to the NASH CRN classification) without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation) at Week 72 in the SEMA+CILO/FIR versus placebo groups
Pharmacokinetics:	The PK of CILO, FIR, and relevant metabolite(s) will be evaluated, as applicable, and plasma concentrations will be provided in a listing.

Statistical Methods:

Efficacy Analysis:	A stratified Mantel-Haenszel test will be used to compare the difference in proportions of participants who achieve a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 72 between the SEMA+CILO/FIR and placebo groups, adjusting for stratification factors.
Safety Analysis:	Safety analyses include summaries of extent of exposure, AEs, laboratory evaluations, and vital sign assessments.
Pharmacokinetic Analysis:	Plasma concentrations of CILO, FIR, and their respective metabolites will be listed, if available. Data from this study may be combined with data from other studies in a population PK meta-analysis.

Sample Size:	The power calculation is based on the estimated proportions of participants in the SEMA+CILO/FIR group to achieve the primary endpoint at Week 72 as compared with the placebo group. Assuming the proportion of participants in the SEMA+CILO/FIR and placebo groups to achieve fibrosis improvement ≥ 1-stage without worsening of NASH at Week 72 is 35% and 12%, respectively, with a sample size of 120 participants in the SEMA+CILO/FIR group and 80 participants in the placebo group, the study has 97% power to detect a difference at a 2-sided significance level of 0.05. If the primary endpoint is achieved, the contribution of CILO/FIR to fibrosis improvement ≥ 1-stage without worsening of NASH will be evaluated by comparing the SEMA+CILO/FIR and SEMA groups for this endpoint. Assuming the proportion of participants to achieve ≥ 1-stage fibrosis improvement without worsening of NASH at Week 72 is 35% and 20% in the SEMA+CILO/FIR and SEMA groups, respectively, with a sample size of 120 participants in each group, the study has 74% power to detect a difference at a 2-sided significance level of 0.05. If the contribution of CILO/FIR to fibrosis improvement ≥ 1-stage without worsening of NASH is demonstrated, the overall effect of NASH resolution will be evaluated by comparing the SEMA+CILO/FIR versus placebo groups. Assuming the proportion of participants in the SEMA+CILO/FIR and placebo groups to achieve NASH resolution at Week 72 is 45% and 10%, respectively, the study has > 99% power to detect a difference at a 2-sided significance level of 0.05. If the superiority of SEMA+CILO/FIR versus placebo for the overall effect of NASH resolution is achieved, the contribution of SEMA to NASH resolution will be evaluated by comparing the SEMA+CILO/FIR and CILO/FIR groups for this endpoint. Assuming the proportion of participants to achieve NASH resolution at Week 72 is 45% and 15% in the SEMA+CILO/FIR and CILO/FIR groups, respectively, with a sample size of 120 participants in each group, the study has 99% power to detect a difference at a 2-sided significance level of 0.05. The power calculations are based on Pearson's chi-square test using a normal approximation.

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ACC	acetyl-coenzyme A carboxylase
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{x\text{-}xx}$	partial area under the concentration versus time curve from time "x" to time "xx"
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
BMI	body mass index
CAP	controlled attenuation parameter
C_{avg}	average observed concentration of drug
CI	confidence interval
CILO	cilofexor (GS-9674)
CK	creatine kinase
CK18 M30	cytokeratin 18 M30 fraction
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
COVID-19	coronavirus disease 2019
CP	Child-Pugh
CPK	creatine phosphokinase
CRF	case report form
CRN	Clinical Research Network
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVOT	cardiovascular outcomes study
CYP	cytochrome P450 enzyme
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
ET	early termination
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FENO	fenofibrate
FGF19	fibroblast growth factor 19
FIR	firsocostat (GS-0976)
FSH	follicle-stimulating hormone
FWER	family-wise type I error rate
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
Gilead	Gilead Sciences/Gilead Sciences, Inc.
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA_{1c}	hemoglobin A_{1c}
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HE	hepatic encephalopathy
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HOMA-IR	homeostasis model assessment of insulin resistance
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IND	investigational new drug
INR	international normalized ratio
IQR	interquartile range
IQR/M	interquartile range/median value

IRB	institutional review board
IRT	Interactive Response Technology
JP	Japanese Pharmacopeia
LDL	low-density lipoprotein
LSM	least-squares mean
MACE	major adverse cardiac event(s)
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MRE	magnetic resonance elastography
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
NAFLD	nonalcoholic fatty liver disease
NAS	nonalcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
NOAEL	no observed adverse effect level
oz	ounce
PBC	primary biliary cholangitis
PD	pharmacodynamic(s)
PE	physical examination
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
Ph. Eur.	European Pharmacopeia
PI	principal investigator
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PS	Patient Safety
PSC	primary sclerosing cholangitis
PT	preferred term
PTM	placebo-to-match
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
RT-PCR	reverse transcriptase-polymerase chain reaction
SADR	serious adverse drug reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SDV	source data verification
SEL	selonsertib (GS-4997)
SEMA	semaglutide

SF-36	36-Item Short Form Survey
SOC	system organ class
SOP	standard operating procedure
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time (observed time point) of C_{max}
ULN	upper limit of normal
US, USA	United States, United States of America
USP	United States Pharmacopeia
VAS	icosapent ethyl (Vascepa®)
VLDL	very low-density lipoprotein

1. INTRODUCTION

1.1. Background

Chronic liver disease and the consequences of end-stage liver disease are increasing globally despite improved prevention and treatment of viral hepatitis. This is due to the emerging epidemics of obesity, metabolic syndrome, and type 2 diabetes that are leading to an increased incidence of nonalcoholic fatty liver disease (NAFLD). Nonalcoholic fatty liver disease is characterized by the excess accumulation of lipid droplets within the liver, also known as hepatic steatosis. Prevalence rates of NAFLD range from 6% to 37% worldwide {Ong 2007, Vernon 2011} with a recent reported pooled global prevalence of 25% {Younossi 2016}.

The aggressive form of NAFLD, nonalcoholic steatohepatitis (NASH), is present in approximately 30% of NAFLD patients and is associated with increased liver-related mortality {Younossi 2016}. Pathologically, NASH is characterized by inflammation and hepatocellular ballooning, with or without fibrosis{Ong 2007, Williams 2011}. In the United States (US), it has been estimated that 3% to 6% of the population {Vernon 2011}, or the equivalent of approximately 15 million adults, have NASH. Modeling of NASH prevalence across 4 European Union (EU) countries (France, Germany, Italy, Spain) projects the prevalence of NASH to increase from 2.6% to 4.4% in 2016 to 5.0% to 6.3% in 2030, which translates to 2.7 to 4.7 million cases across these countries in 2030 {Estes 2018}. Furthermore, as NASH is a manifestation of metabolic syndrome, risk factors for cardiovascular disease are frequent comorbidities in this patient population {Dietrich 2014, Faramawi 2008, Voulgari 2010}, and thus cardiovascular outcomes are also relevant. Given the absence of any approved therapies for patients with advanced fibrosis due to NASH, and the increasing prevalence of NASH comorbidities, NASH is expected to represent an increasingly large unmet medical need.

Nonalcoholic steatohepatitis is thought to occur as the result of metabolic syndrome: the impact of obesity, insulin resistance, and dyslipidemia in the liver. Nonalcoholic steatohepatitis is the result of a chronic state of hepatocyte cell death and activation of sterile innate immune pathways leading to a vicious cycle of inflammation, liver injury, and ultimately, fibrosis. Increased circulating bile acids and excessive accumulation of lipids within hepatocytes are hallmarks of NASH and are each thought to contribute to hepatocyte cell death. Circulating bile acid levels are increased in NASH and contribute to disease progression by promoting tissue damage leading to hepatic inflammation and fibrosis {Donnelly 2005, Neuschwander-Tetri 2010}. Excessive hepatic lipids may result from dysregulated metabolic processes such as increased lipolysis in adipose tissue and flux of non-esterified fatty acids to the liver, increased hepatic de novo lipogenesis (DNL), reduced mitochondrial function, and/or insufficient β-oxidation of fatty acids in the liver {Donnelly 2005, Lambert 2014, Neuschwander-Tetri 2010}. Lipotoxic intermediates derived from fatty acids are thought to contribute to the etiology of NASH {Neuschwander-Tetri 2010}.

Over time, in the setting of persistent risk factors, fibrosis due to NASH may progress to an advanced stage, specifically bridging fibrosis or cirrhosis, with the latter occurring in 10% to 20% of patients. Advanced fibrosis due to NASH is characterized by extensive collagen deposition and remodeling of the extracellular matrix, driven predominantly by activation of hepatic stellate cells {Mederacke 2013}. Clinically, advanced fibrosis is associated with increased morbidity and mortality {Ekstedt 2015, Yeh 2014}. Cirrhosis increases the risk of hepatocellular carcinoma (HCC) and other complications of end-stage liver disease, including jaundice, fluid retention (edema and ascites), portal hypertension and variceal bleeding, impaired coagulation, and hepatic encephalopathy (HE). Decompensated liver disease, as defined by the development of 1 of the above complications, has a high mortality rate and the only known effective treatment is liver transplantation. Given the increasing prevalence of obesity and obesity-related diseases in the US, as of 2016, NASH is the leading indication for liver transplantation among women and the second leading indication among men {Noureddin 2018}. Among patients undergoing liver transplant for HCC, NASH is the leading etiology {Afzali 2012, Wong 2014}.

1.2. Semaglutide

Please refer to the investigator's brochure (IB) for further information on semaglutide (SEMA) not included below.

1.2.1. General Information

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) developed by Novo Nordisk A/S for weight management and is under investigation for treatment of NASH at a dose of 2.4 mg once weekly. Semaglutide at doses of 0.5 mg and 1.0 mg once weekly has been approved as an adjunct to diet and exercise for the management of type 2 diabetes and to reduce the risk of major adverse cardiac events (MACE) in adults with type 2 diabetes and established cardiovascular disease under the trade name, Ozempic®.

Semaglutide is based on the same technology as used for liraglutide (Victoza®, Saxenda®), with fatty acid acylation and albumin binding as the protraction principle, and with maintained high homology to human GLP-1. Semaglutide has been modified resulting in a longer half-life suitable for once-weekly dosing and is stabilized against degradation by the DPP-4 enzyme. The extended half-life of the SEMA molecule is primarily obtained by increased albumin binding, which is facilitated by a large fatty acid-derived chemical moiety.

1.2.2. Nonclinical Pharmacology and Toxicology

Nonclinical efficacy data have shown that SEMA lowers blood glucose, food intake, and body weight in animal models of diabetes and obesity. Furthermore, SEMA attenuated the development of atherosclerosis and had an anti-inflammatory action in the cardiovascular system. In a mouse model of NAFLD, SEMA reduced liver triglyceride levels, expression of collagen genes, and inflammation markers. Semaglutide exerts its actions through the GLP-1 receptor using similar pathways and with similar cellular actions as native GLP-1. The mechanism of action is consistent with that of other long-acting GLP-1 RAs, for example liraglutide.

The general toxicology program comprised studies in mice, rats and monkeys of up to 13, 26, and 52 weeks, respectively. In all 3 species, dose levels were limited by the pharmacological effects on food intake and body weight. The majority of the treatment-related changes were considered to be due to the pharmacological effects of SEMA. Non-lethal thyroid C-cell tumors observed in rodents are a class effect for the GLP-1 RAs. In 2-year carcinogenicity studies in rats and mice, SEMA caused thyroid C-cell tumors at clinically relevant exposures. The C-cell changes in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. Recent data have shown that the GLP-1 receptor is not expressed in normal human thyroid C-cells. Accordingly, the human relevance of rodent C-cell tumors is considered low but cannot be completely excluded.

Semaglutide adversely affected embryofetal development in the rat by a GLP-1 receptor-mediated impaired function of the inverted yolk sac placenta during a period of gestation when the rat embryo is entirely dependent on the yolk sac placenta for its nutrient supply. Due to species differences in yolk sac anatomy and function, and due to the lack of GLP-1 receptor expression in cynomolgus monkey yolk sac, this mechanism is considered unlikely to be of relevance to humans. Involvement of additional mechanisms cannot be excluded. In rabbits and monkeys, increased number of pregnancy losses and slightly increased incidences of fetal abnormalities, which did not resemble the findings in rats, were observed. These findings might be incidental or related to the markedly reduced maternal body weight; however, relevance to humans cannot be completely excluded for these findings.

1.2.3. Clinical Studies of Semaglutide

1.2.3.1. Diabetes

As part of the type 2 diabetes development program, SEMA administered subcutaneously (SC) once weekly was evaluated in 8 Phase 3 studies (including a 2-year cardiovascular outcomes study [CVOT]). Across all Phase 3 efficacy studies, both SEMA SC 0.5 mg and 1.0 mg were superior in lowering glycosylated hemoglobin A_{1c} (HbA_{1c}) and body weight as compared with placebo (both as monotherapy and in combination with insulin) or compared with the respective marketed comparators. Cardiovascular safety of SEMA SC was established in the CVOT with an estimated hazard ratio for SEMA SC versus placebo of 0.74 (95% CI: 0.58-0.95) corresponding to a reduced risk of MACE by 26% versus placebo.

The pharmacokinetic (PK) and pharmacodynamic (PD) properties of SEMA SC once weekly were investigated as part of the type 2 diabetes development program including a total of 16 clinical pharmacology studies. Semaglutide has PK properties compatible with once-weekly administration with a median time to maximum concentration (T_{max}) of 1 to 3 days and an elimination half-life ($t_{1/2}$) of approximately 1 week. The exposure of SEMA in participants with various degrees of impaired renal function and with various degrees of impaired hepatic function was similar to the exposure in participants with normal renal function and normal hepatic function, respectively. No clinically relevant drug-drug interactions (DDIs) were observed between SEMA and any of the orally administered compounds tested (including metformin, warfarin, digoxin, atorvastatin and oral contraceptive combination drugs) and thus, no dose adjustments of the orally administered study drug are required. Semaglutide circulates in plasma, highly bound to plasma protein. Prior to excretion, SEMA is metabolized and excreted in urine and feces, with only 3% of the administered dose excreted as intact SEMA.

The established safety profile of SEMA SC 0.5 mg and 1.0 mg once weekly in type 2 diabetes is consistent with the GLP-1 RA drug class in general. Semaglutide SC is associated with a higher frequency of gastrointestinal (GI) adverse events (AEs) compared with placebo and active comparators. Gastrointestinal AEs generally occur early during dose escalation, are mild or moderate in severity and resolve without sequelae. Known or potential risks identified with SEMA SC in type 2 diabetes include cholelithiasis, pancreatic abnormalities (including pancreatitis), neoplasms and diabetic retinopathy complications. Cholelithiasis occurred more frequently with SEMA SC than with comparators, though the absolute risk was low; few of the events were serious and they did not appear to be preceded by a large and rapid weight loss. No concerns were identified for pancreatic safety and no causal association between SEMA SC and any type of neoplasm has been observed in the type 2 diabetes development program.

Data from the CVOT in type 2 diabetes showed that SEMA SC treatment was associated with an increased risk of diabetic retinopathy complications in participants with preexisting diabetic retinopathy, albeit at low risk. This finding is believed to be attributable to the rapid initial improvement in blood glucose levels with SEMA, consistent with the early worsening phenomenon described with insulins. Given these findings, patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines, and patients with unstable diabetic retinopathy are excluded from this study. Of note, a Phase 3 study (FOCUS; NN9535-4352) is ongoing to evaluate the long-term effects of SEMA SC, compared with placebo, on diabetic eye disease in participants with type 2 diabetes.

1.2.3.2. Weight Management

Novo Nordisk A/S conducted a Phase 2 dose-finding clinical study of SEMA SC treatment in 857 participants with obesity (NN9536-4153). Eligible participants were randomized to a target daily dose of SEMA 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg, liraglutide 3.0 mg, or corresponding placebo-to-match (PTM) in each of the active treatment arms. Overall, a dose-dependent decrease in body weight was observed at Week 52, with the greatest weight loss (−13.84% estimated mean change in body weight from baseline) observed at the highest SEMA dose tested (0.4 mg once daily). No unexpected safety findings were identified, and the

tolerability and safety profiles were consistent overall with previous findings in the SEMA SC development program for type 2 diabetes and the GLP-1 RA class in general. The most frequently reported AEs were GI disorders (mainly nausea). Results from this Phase 2 study showed that the SEMA 0.4 mg once-daily dose was the most effective in terms of weight loss while displaying an acceptable tolerability profile. The rationale for the equivalence of SEMA 0.4 mg SC daily dose with 2.4 mg SC weekly dose is presented in Section 1.7.

For the evaluation of SEMA in weight management, Novo Nordisk A/S completed a Phase 3a clinical study program utilizing SEMA 2.4 mg SC treatment in participants with obesity (the Semaglutide Treatment Effect in People With Obesity [STEP] program). In the pivotal study (NN9536-4373), SEMA led to a statistically significant reduction in body weight compared with placebo at Week 68. Participants treated with SEMA achieved a weight loss of 14.9%, from a mean baseline body weight of 105.3 kg, compared with a 2.4% weight loss with placebo. In addition, 86.4% of those who received SEMA achieved weight loss of 5% or more after 68 weeks, compared with 31.5% with placebo. In this study, SEMA appeared to be safe and well tolerated. The most common AEs among participants treated with SEMA were GI events, most of which were transient, and mild or moderate in severity. Based on the Phase 3a study data, SEMA was approved for a weight management indication in the US and EU.

1.2.3.3. NASH

As of 15 February 2021, the clinical development program for SEMA SC monotherapy for the treatment of NASH comprises 1 completed Phase 1 study (in participants with NAFLD), 1 completed Phase 2 study (in participants with F1-F3 fibrosis due to NASH), 1 completed Phase 2 study (in participants with NASH and compensated F4) and 1 ongoing Phase 3 study (in participants with NASH and F2-F3). Completed Phase 1 and 2 studies are described in full in the SEMA IB; brief summaries of the results from the completed Phase 2 NASH studies follow below.

In the Phase 2 NASH Study NN9931-4492, 71 participants with cirrhosis (F4 fibrosis) due to NASH were randomized to receive SEMA 2.4 mg (47 participants), or placebo (24 participants) as once-weekly SC injections {Loomba 2023}. After randomization, the participants entered a dose-escalation period, with dose increases every 4 weeks until the target dose was reached.

The mean age of the study population was 59.5 years, 69% were women, and 87% were White. At baseline the mean body mass index (BMI) was 34.9 kg/m^2 and 75% had type 2 diabetes, with a mean HbA_{1c} of 7.1%. Use of glucose-lowering medication was generally well balanced between the groups. Histological parameters and baseline liver parameters were also generally balanced between treatment groups, though the SEMA group contained a greater number of participants with Ishak score 6/6 at baseline. Participants had a mean nonalcoholic fatty liver disease activity score (NAS) of 4.8, more than 75% of participants overall had an Ishak score of 6/6, the mean baseline Model for End-Stage Liver Disease (MELD) score was 7.6, and mean albumin level was 4.2 g/dL.

At 48 weeks there was no significant difference in the proportion of patients in each group with improvement in liver fibrosis without worsening of NASH. There was no significant difference in the proportion of patients in each group with NASH resolution or for components of NASH between treatment groups. Change in liver stiffness by magnetic resonance elastography (MRE) from baseline was not significantly different between groups. Improvement in liver steatosis by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) from baseline was significantly greater in the SEMA group (49% with ≥ 30% reduction) than in the placebo group (13% with ≥ 30% reduction), accompanied by greater reduction in liver fat volume and thus total liver volume in the SEMA group. Reductions in the liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) from baseline were significantly greater in the SEMA group compared with placebo over 48 weeks of treatment. Reductions in Pro-C3 and high-sensitivity C-reactive protein (CRP) levels were also significantly greater in the SEMA group versus placebo. Greater reduction in enhanced liver fibrosis (ELF) was observed in the SEMA group over 48 weeks compared with placebo, though the difference between groups was not significant. Body mass index and waist circumference were significantly lower with SEMA versus placebo at Week 48, and, among patients with type 2 diabetes, a significantly greater reduction in HbA_{1c} and fasting plasma glucose from baseline was observed in the SEMA group compared with the placebo group. Reductions in levels of triglycerides and very low-density lipoprotein (VLDL) cholesterol from baseline were significantly greater with SEMA than with placebo, but this was not the case for low-density lipoprotein (LDL) or total cholesterol. Blood pressure was reduced from baseline in patients who received SEMA at 24 weeks but increased again and was not significantly different to placebo at 48 weeks.

A total of 48 weeks of treatment with SEMA SC 2.4 mg once weekly was safe and well tolerated in this compensated cirrhotic NASH population. Overall, the safety profile of SEMA seen in this study was consistent with previous studies in patients with type 2 diabetes, obesity, and NASH, with mild to moderate, transient GI effects accounting for most on-treatment AEs. No effects were observed on hepatic or renal function with SEMA treatment, and although the study was not powered to assess decompensating events, no decompensating events were observed during the study period. Similar proportions of patients experienced AEs (42 [89%] patients in the SEMA group and 19 [79%] in the placebo group, of which 6 [13%] and 2 [8%], respectively, were serious). No serious events were considered related to study drug and there were no deaths during the study. Most AEs were mild or moderate in severity, but there were 8 severe events in the SEMA group versus 1 in the placebo group; additionally, more AEs in the SEMA group than in the placebo group were judged as possibly or probably related to study drug. No patients withdrew from the study due to AEs. A total of 5 patients had 8 AEs leading to dose reduction (6 AEs in 4 patients in the SEMA group, and 2 AEs in 1 patient in the placebo group). Three patients had AEs leading to premature treatment discontinuation (2 with GI disorders [nausea] considered probably related to treatment and 1 with an eye disorder [vitreous detachment] considered unlikely related to treatment), all in the SEMA group. In total, 64 (90%) patients completed treatment, and 3 patients (2 in the SEMA group and 1 in the placebo group) withdrew from the study.

This study was limited by a relatively small sample size and relatively short treatment duration but did not raise any new safety concerns and demonstrated overall improvement in cardiometabolic parameters and noninvasive markers of liver fat and liver injury with SEMA treatment.

In the Phase 2 NASH Study NN9931-4296, 320 participants with F1-F3 fibrosis due to NASH were randomized to receive SEMA 0.1 mg (80 participants), SEMA 0.2 mg (78 participants), SEMA 0.4 mg (82 participants), or placebo (80 participants) as once-daily SC injections. After randomization, the participants entered a dose-escalation period, with dose increases every 4 weeks until the target dose was reached.

The mean age of the study population was 55 years, 60.6% were women, and 77.5% were White. At baseline, the mean BMI was 35.8 kg/m^2 and the mean body weight was 98.4 kg, which was similar across treatment groups. Approximately 62% of the participants had type 2 diabetes at baseline, with a mean duration of 7.5 years and a mean HbA_{1c} value of 7.3%. Approximately half of the participants (49.4%) had fibrosis stage 3 and approximately a quarter each had fibrosis stages 1 or 2. Overall, the majority of participants had a total NAS of 4 (41.6%), 5 (35.6%), or 6 (18.4%), with a mean NAS of 4.9, similar across treatment groups. In the overall population, baseline noninvasive tests of liver fibrosis included a mean ELF™ score of 9.8, and a mean liver stiffness by vibration-controlled transient elastography (FibroScan®) of 12.2 kPa. Mean liver enzyme values (ALT: 63 U/L, AST: 49 U/L, GGT: 85 U/L) at baseline were slightly elevated compared with reference ranges.

The proportion of participants with F2 or F3 fibrosis who achieved NASH resolution with no worsening in liver fibrosis at Week 72 was statistically significantly higher in the SEMA groups than in the placebo group, and highest in the SEMA 0.4 mg group (58.9% vs 17.2% in the placebo group). The proportion of participants with F2 or F3 fibrosis who achieved a ≥ 1-stage improvement in liver fibrosis without worsening of steatohepatitis at Week 72 was higher in the SEMA 0.1 mg and 0.4 mg groups, and similar in the SEMA 0.2 mg group, compared with the placebo group, but the differences were not statistically significant. The liver enzymes ALT, AST, and GGT showed a dose-dependent decrease from baseline to Week 72 in all treatment groups, with the greatest reductions observed with the SEMA 0.4 mg daily dose. The reductions in body weight showed a dose-response relationship, with the greatest reduction in the SEMA 0.4 mg group (−12.51% vs −0.61% in the placebo group). At Week 72, the reductions in HbA_{1c} were statistically significantly greater in each of the SEMA groups than in the placebo group, with the greatest treatment differences in the SEMA 0.2 mg and 0.4 mg groups. Semaglutide generally increased levels of high-density lipoprotein (HDL) cholesterol and reduced levels of free fatty acids, triglycerides and VLDL cholesterol from baseline to Week 72. The changes in HDL cholesterol, free fatty acids, triglycerides, and VLDL cholesterol at Week 72 statistically significantly favored SEMA 0.4 mg daily dose over placebo.

A total of 72 weeks of treatment with SEMA SC 0.1 mg, 0.2 mg, or 0.4 mg once daily was safe and well tolerated in this noncirrhotic NASH population. The observed safety and tolerability profile was consistent with that of SEMA SC in type 2 diabetes and weight management and with the GLP-1 RA drug class in general. No dose relationship among the SEMA SC group was

observed for AEs leading to treatment discontinuation; a higher proportion of participants discontinued treatment due to AEs in the SEMA SC 0.2 mg group (12.8%) than in the other treatment groups (ranging between 3.8% and 5.0%). Serious AEs (SAEs) were reported by a higher proportion of participants in all SEMA SC groups (range: 14.8% to 19.2%) than in the placebo group (10.0%) but with no dose-relationship among the SEMA SC groups. The most frequently reported AEs were GI disorders which were reported by a higher proportion of participants in all SEMA SC groups (range: 63.8% to 76.9%) than with placebo (45.0%). Nausea, the most frequent GI AE, increased dose-dependently with SEMA SC. There were no apparent dose-dependent findings for any other safety parameters. Hepatic events were reported by a lower proportion of participants with SEMA SC (range: 7.7% to 11.3%) than with placebo (13.8%), whereas gallbladder-related disorders were reported by a higher proportion of participants exposed to SEMA SC (range: 5.1% to 7.4%) than with placebo (2.5%). Neoplasms (benign, malignant, unspecified including cysts and polyps) were reported by 12.5% to 17.3% of the participants in the SEMA SC groups and by 7.5% in the placebo group. Except for events of large intestine polyp and renal cysts, which were mostly incidental findings, there was no notable pattern with respect to organ system of origin or distribution between treatment groups. Increases in amylase and lipase were observed with SEMA SC and are well known from other GLP-1 RAs. No events of acute pancreatitis were reported.

Of note, acute pancreatitis is considered a risk associated with the use of the GLP-1 RA class, therefore, patients with a history of chronic pancreatitis or recent acute pancreatitis are excluded from this study. No causal association between SEMA and any type of neoplasm has been seen in the clinical development program.

1.3. Cilofexor

Please refer to the current IB for cilofexor (CILO; GS-9674) for further information not included below.

1.3.1. General Information

Cilofexor is a potent and selective agonist of the farnesoid X receptor (FXR) whose activity in intestinal epithelial cells results in the release of fibroblast growth factor 19 (FGF19). FGF19 is an endocrine peptide which drives a signaling cascade to decrease lipogenesis, gluconeogenesis, hepatic triglyceride accumulation, and bile acid synthesis. Given the role of metabolic dysregulation and bile acid homeostasis in NASH pathogenesis, activation of FXR with CILO is expected to improve NASH. Cilofexor as a single agent has also been evaluated in participants with primary biliary cholangitis (PBC), and in Phase 2 and Phase 3 studies in participants with primary sclerosing cholangitis (PSC).

1.3.2. Nonclinical Pharmacology and Toxicology

The nonclinical toxicity profile of CILO and its major metabolites (GS-716070 and GS-1056756) were assessed in mice, rats, and cynomolgus monkeys administered CILO orally for up to 26, 13, and 39 weeks, respectively (Studies TX-402-2009; TX-402-2010; TX-402-2025). Findings attributed to CILO administration were primarily related to the liver (increases in alkaline phosphatase [ALP]; decreases in serum bile acids, cholesterol, and

triglycerides; increases in liver weight; and hepatocellular hypertrophy). These findings were minimal to mild, nonadverse, and reversible after discontinuation of treatment. The no observed adverse effect levels (NOAELs) in the repeat-dose toxicity studies were associated with exposure margins ≥ 12 times higher than the human exposure at the 30 mg dose. Cilofexor and its major metabolites are nongenotoxic and CILO was noncarcinogenic in a 2-year mouse carcinogenicity study. In the 2-year rat carcinogenicity study, there was an increased incidence in hepatocellular adenomas and carcinomas in males at all CILO doses (ie, ≥ 250 mg/kg/day) and in females at 1000 mg/kg/day (highest dose tested). Also, there was an increased incidence of hepatocholangiocellular adenoma at ≥ 500 mg/kg/day, and hepatocholangiocellular carcinoma at 1000 mg/kg/day in male rats. The clinical relevance of these findings is unknown given the lack of similar findings in mice and the predominance of findings in male rats. The mechanism for the liver tumors associated with CILO is unknown; however, CILO does not have activity through known carcinogenic mechanisms with relevance to humans (DNA reactivity, estrogenic activity, cytotoxicity, infection, iron overload).

There was no effect on embryofetal development in mice and rabbits at doses of up to 300 mg/kg/day in mice (Studies TX-402-2016; TX-402-2017) and 200 mg/kg/day in rabbits (Study TX-402-2018). These doses were associated with exposures that are 49- and 47-fold higher than the human exposure ($AUC_{0\text{-}24h}$) at the 30 mg once-daily dose based on a preliminary population PK model of NASH. The decreased fetal weights observed at 1000 mg/kg/day in the pregnant rabbit dose range–finding study were attributed to maternal toxicity and not a direct fetal effect (Study TX-402-2015).

In addition, GS-1056756, a prominent metabolite of CILO, had no effect on embryofetal development in mice at 300 mg/kg/day (Study TX-402-2033), corresponding to 2-fold higher than the human exposure ($AUC_{0\text{-}24h}$) at the 30 mg once-daily dose based on a preliminary population PK model of NASH.

Decreased fertility and copulation/conception indices and longer mean pre-coital interval was noted at 300 mg/kg/day (highest dose evaluated) as compared with controls (Study TX-402-2022). There were no effects on male or female fertility at 60 mg/kg/day. This dose was associated with exposures in male and female mice that were 12- and 19-fold higher, respectively, than the human exposure ($AUC_{0\text{-}24h}$) at the 30 mg once-daily dose. Also, there were no effects on early embryonic development at up to 300 mg/kg/day. This dose was associated with exposures in male and female mice that were 37- and 93-fold higher, respectively, than the human exposure ($AUC_{0\text{-}24h}$) at the 30 mg once-daily dose.

Drug-drug interaction study data do not suggest a potential for interaction with hormones used for contraception.

1.3.3. Clinical Studies of CILO

As of 22 September 2022, across all indications, 9 Phase 1 studies and 6 Phase 2 studies were completed. One Phase 3 clinical study was terminated after the results of a planned futility analysis did not satisfy the predefined efficacy criteria in participants with PSC (Study GS-US-428-4194). Completed Phase 1 and 2 studies are described in full in the IB; a brief summary of clinical pharmacology results from relevant prior studies follows. Results from completed clinical studies (GS-US-384-3914, GS-US-454-4378, and GS-US-454-5533) including CILO in combination with firsocostat (FIR; GS-0976) and/or SEMA are presented in Section 1.5.2.

Following single and multiple oral doses (10 to 300 mg) in healthy participants (Study GS-US-402-1851), CILO was rapidly absorbed with minimal to no accumulation observed at steady state, consistent with the median half-life of 10 to 15 hours. GS-716070 (CILO metabolite with > 40-fold less potency than CILO against FXR) exhibited a steady-state metabolite-to-parent AUC ratio of 0.57, with plasma PK mirroring trends observed for CILO with respect to linearity and accumulation. A second metabolite of CILO, GS-1056756, exhibited an AUC accumulation ratio of 11.4 on Day 14, consistent with its long half-life (approximately 175 h) and a metabolite-to-parent AUC ratio of approximately 0.86 (Study GS-US-402-1851). Cilofexor and GS-716070 exposures in participants with NASH were higher (approximately 2- to 3-fold) than those observed in healthy participants, whereas GS-1056756 concentrations were similar in participants with NASH compared with healthy participants. Administration of a single oral 100 mg dose of CILO (Study GS-US-454-5280) indicated that the effect of food on CILO PK is meal-type dependent; CILO AUC_{inf} was 35% lower or 9% lower when administered with a light- or high-fat meal, respectively. These data support dosing of CILO without regard to food.

Across the range of CILO doses evaluated (10 to 300 mg once daily), doses ≥ 30 mg provide comparable intestinal FXR agonism as assessed by increases in plasma FGF19 exposure. Exposure-response relationships show that changes in C4 exposure are negatively correlated with changes in exposures of FGF19 and CILO.

Cilofexor was administered at doses up to 300 mg in Phase 1 studies. In Study GS-US-402-1851, CILO was well tolerated in healthy adult participants at doses up to 300 mg once daily for up to 14 days. The incidence of AEs did not increase with ascending doses of CILO, and no dose-dependent toxicities were noted.

In the Phase 1 Study GS-US-402-3885, CILO 30 mg and 10 mg single-dose administration was well tolerated in participants with normal or impaired hepatic function. Based on the available overall exposure-safety profile of CILO, dose adjustments are not considered necessary in participants with mild hepatic impairment. Limited clinical safety data are available at the free exposures observed in participants with moderate or severe hepatic impairment. As such, participants with moderate or severe hepatic impairment are excluded from the current study.

In 4 completed Phase 2 studies in NASH (Studies GS-US-402-1852, GS-US-454-4378, GS-US-454-5533, GS-US-384-3914), 1 completed Phase 2 study in PBC

(Study GS-US-427-4024), and 1 completed Phase 2 study in PSC (Study GS-US-428-4025), CILO 30 mg and 100 mg as monotherapies appear to be well tolerated, and incidences of Grade 3 AEs, discontinuations due to AEs, and SAEs were similar to those observed in the participants in the placebo group. Rash and pruritus are common and very common, respectively, among NASH patients.

1.4. Firsocostat

Please refer to the current FIR IB for further information not included below.

1.4.1. General Information

Firsocostat is a small molecule allosteric inhibitor that acts at the protein-protein homodimer interface of acetyl-coenzyme A carboxylases (ACC) ACC1 and ACC2 to prevent dimerization. ACC1 and ACC2 are important regulators of fatty acid metabolism. ACC1 catalyzes the first step of DNL by converting acetyl-coenzyme A to malonyl coenzyme A while ACC2 regulates the entry of fatty acids into the mitochondria where beta oxidation can occur. Therefore, inhibition of ACC1 and ACC2 will reduce DNL and increase fatty acid beta oxidation, respectively.

1.4.2. Nonclinical Pharmacology and Toxicology

Firsocostat has been characterized in several biochemical and cellular assays to enhance the understanding of the mechanism of action in vivo, in several mechanistic models to demonstrate target engagement, and in animal disease models to demonstrate activity on endpoints relevant to metabolic disease. Moreover, extensive safety pharmacology and receptor screening studies have been conducted.

The results of these PD studies indicate that FIR can reduce the DNL, hepatic steatosis, insulin resistance, and fibrosis produced in nonclinical models of metabolic disease and fibrosis without adversely affecting food consumption or markers of liver function.

As described in the FIR IB, GS-834356, a liver-targeted ACC inhibitor and analog of FIR, reduced steatosis in a murine model of NASH induced by a diet enriched in fat, cholesterol, and fructose (fast food diet, FFD). In this model, ACC inhibition by GS-834356 dose-dependently reduced hepatic steatosis, liver triglycerides and cholesterol, plasma ALT and AST, and markers of hepatic fibrosis and fibrogenesis, but also dose-dependently increased plasma triglycerides. GS-834356 also decreased hepatic triglycerides and increased plasma triglycerides in a rat high-fat, high-sucrose model of hepatic steatosis. These findings are consistent with a recent report that pharmacologic or genetic inhibition of ACC in the liver decreases hepatic triglyceride levels and increases plasma triglyceride levels {Goedeke 2018, Kim 2017}. GS-834356 also significantly inhibited fibrosis progression over 6 weeks of treatment in the rat choline-deficient high-fat diet model of advanced fibrosis {Bates 2020}.

The nonclinical toxicologic profile of FIR and its major metabolite (GS-834773) has been well characterized in single- and repeat-dose toxicity studies up to 39 weeks in duration and in genetic toxicity, carcinogenicity, fertility and embryofetal developmental toxicity, phototoxicity, and local tolerance studies. The primary target organ toxicity was the presence of cataracts in dogs based on ophthalmic and histological examinations at doses of ≥ 60 mg/kg/day and lens degeneration in mice at 15 mg/kg/day. The NOAELs in the repeat-dose toxicity study were associated with exposure margins ≥ 3 times higher than the clinical exposure at the 20 mg dose. Additionally, FIR and its major metabolite were nongenotoxic and FIR was noncarcinogenic in 2-year rat carcinogenicity study. There were no effects on embryofetal development at exposures 24 and 121 times the clinical exposure in rats and rabbits, respectively. Firsocostat was nonphototoxic and was also considered noncorrosive and does not require classification as an eye irritant.

No formal studies have been conducted to evaluate the reproductive toxicity of FIR; therefore, the reproductive toxicity of FIR in humans is unknown. However, mutant mice lacking ACC1, one of the targets of FIR, are embryonically lethal. Therefore, FIR is contraindicated in pregnancy. Nonclinical data in human hepatocytes indicate that FIR is a mild inducer of cytochrome P450 enzyme (CYP) 3A4 isoenzymes. Clinical data demonstrates no decrease in exposure of a representative oral hormonal contraceptive indicating no loss of contraceptive efficacy is expected upon administration of FIR with hormonal contraceptives.

1.4.3. Clinical Studies of FIR

As of 22 September 2022, 12 Phase 1 and 3 Phase 2 clinical studies including FIR have been completed. Completed Phase 1 and 2 studies are described in full in the IB; a brief summary of clinical pharmacology results from relevant prior studies follows below. Results from completed clinical studies (GS-US-454-4378, GS-US-454-5533, and GS-US-384-3914) including FIR in combination with CILO and/or SEMA are presented in Section 1.5.2 and 1.5.3.

Following single and multiple oral doses (20 to 1000 mg) in healthy participants, FIR was rapidly absorbed with minimal to no accumulation of FIR observed at steady state, consistent with a median half-life of approximately 5 to 10 hours. Firsocostat exhibited approximately dose-proportional PK over the clinically relevant dose range (20 to 500 mg). GS-834773, a glucuronide conjugate metabolite of FIR, exhibited a steady-state metabolite-to-parent AUC ratio of 0.1, with plasma PK mirroring trends observed for FIR with respect to linearity and accumulation. Food alters the rate of absorption, as evidenced by changes in FIR and GS-834773 C_{max} but does not alter the extent of absorption (no change in AUC); FIR may be administered without regard to food.

In obese, but otherwise healthy, male participants in whom DNL was stimulated with fructose, FIR demonstrated dose-dependent inhibition of fractional DNL, with reductions (relative to placebo) of change from baseline in fractional DNL as a function of the area under effect curve of approximately 70%, 85%, and 104% following administration of 20, 50, and 200 mg FIR, respectively. A similar reduction in fractional DNL (68% inhibition relative to baseline) was observed in healthy participants not administered fructose who received FIR 20 mg once daily.

Overall, FIR as a monotherapy has been well tolerated. The majority of AEs reported in healthy participants and participants with NASH were Grade 1 or Grade 2 in severity and resolved by study completion. The most frequently reported AEs were nausea, abdominal distention, abdominal pain, constipation, diarrhea, abdominal tenderness, dyspepsia, and vomiting. Triglyceride elevations were observed in a repeat-dose study (0976-102) in healthy participants and in participants with NASH who received FIR 20 mg (Studies GS-US-426-3989, GS-US-384-3914, and GS-US-454-4378).

1.5. CILO/FIR Combination

Please refer to the current CILO/FIR fixed-dose combination (FDC) IB for further information not provided below.

1.5.1. Nonclinical Pharmacology and Toxicology

Combinations of CILO and the FIR analog GS-834356 had synergistic effects to reduce liver triglycerides and markers of fibrogenesis in the mouse Amylin Liver NASH Diet-induced model of NASH. Further, a combination of CILO and GS-834356 also partially inhibited fibrosis progression over 10 weeks of dosing in the 18-week rat choline-deficient high-fat diet of advanced fibrosis where the monotherapies were no longer efficacious. There were no adverse findings when CILO and FIR were dosed in combination to mice by the oral route for 13 weeks at doses of 20 mg/kg/day of CILO and 3 mg/kg/day of FIR. Exposures to CILO and FIR at these doses were 5 and 4 times higher, respectively, than the exposure to CILO and FIR in humans at the 30 mg and 20 mg doses, respectively.

1.5.2. Clinical Studies Including CILO and FIR in Combination

1.5.2.1. Study GS-US-384-3914

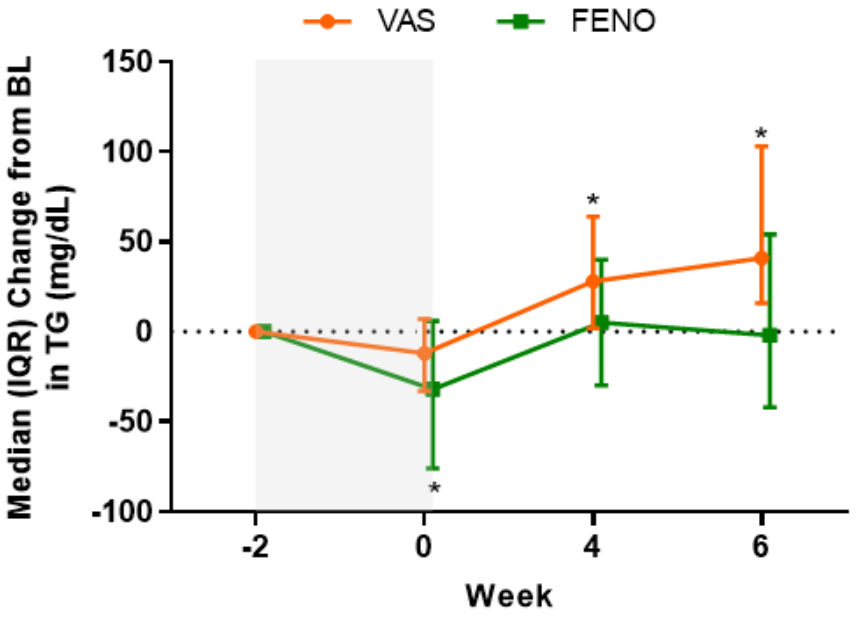
Study GS-US-384-3914 is a completed Phase 2, proof-of-concept, open-label study that evaluated the safety, tolerability, and efficacy of selonsertib (SEL; GS-4997), FIR, and CILO as single agents and combinations in participants with NAFLD/NASH. The study consisted of 13 cohorts, with select cohorts receiving CILO and FIR as monotherapy or in combination. Final results for Cohorts 1 through 11 are included in the IB and safety and efficacy results for Cohorts 12 and 13 are presented below.

1.5.2.1.1. Triglyceride Laboratory Evaluations in Participants Treated With CILO+FIR and Icosapent Ethyl (Vascepa®; VAS) or Fenofibrate (FENO) (Study GS-US-384-3914 Cohorts 12 and 13)

Participants with suspected NASH and fibrosis, as determined by biopsy or liver stiffness by transient elastography (≥ 9.9 kPa or MRE ≥ 2.88 kPa) with serum triglycerides ≥ 150 and < 500 mg/dL were randomized to treatment with VAS 2 g twice daily (Cohort 12; n = 33) or FENO 145 mg daily (Cohort 13; n = 33) for 2 weeks (starting on Day −14) followed by the addition of FIR 20 mg + CILO 30 mg daily on Day 1 for 6 weeks. Randomization was stratified by screening triglycerides (< 250 mg/dL vs ≥ 250 mg/dL). Safety results and triglyceride laboratory evaluations for Cohorts 12 and 13 as of 29 January 2021 are presented below.

The median (first quartile [Q1], third quartile [Q3]) age of participants in Cohorts 12 and 13 was 55 (46, 63) years and most participants had diabetes (69.4%) and were obese (82%). At baseline (Day −14), median (Q1, Q3) triglycerides were 177 mg/dL (154, 205) in Cohort 12 and 190 mg/dL (144, 258) in Cohort 13, including 13% and 31% with triglycerides ≥ 250 mg/dL, respectively. After 2 weeks of VAS or FENO monotherapy, median changes in triglycerides were −12 mg/dL (−33, 7 [$P = 0.0898$ vs baseline]) and −32 mg/dL (−76, 6 [$P = 0.0121$ vs baseline]), respectively. Following 6 weeks of combination treatment with CILO+FIR (in addition to either VAS or FENO), median change from baseline in triglycerides was +41 mg/dL (16, 103 [$P < 0.0001$ vs baseline]) in the VAS group and −2 mg/dL (−42, 54 [$P = 0.9206$ vs baseline]) in the FENO group (Figure 1). In participants with baseline triglycerides ≥ 250 mg/dL, changes at Week 6 were +99 mg/dL (−29, 185) in the VAS group and −61 mg/dL (−128, −8) in the FENO group.

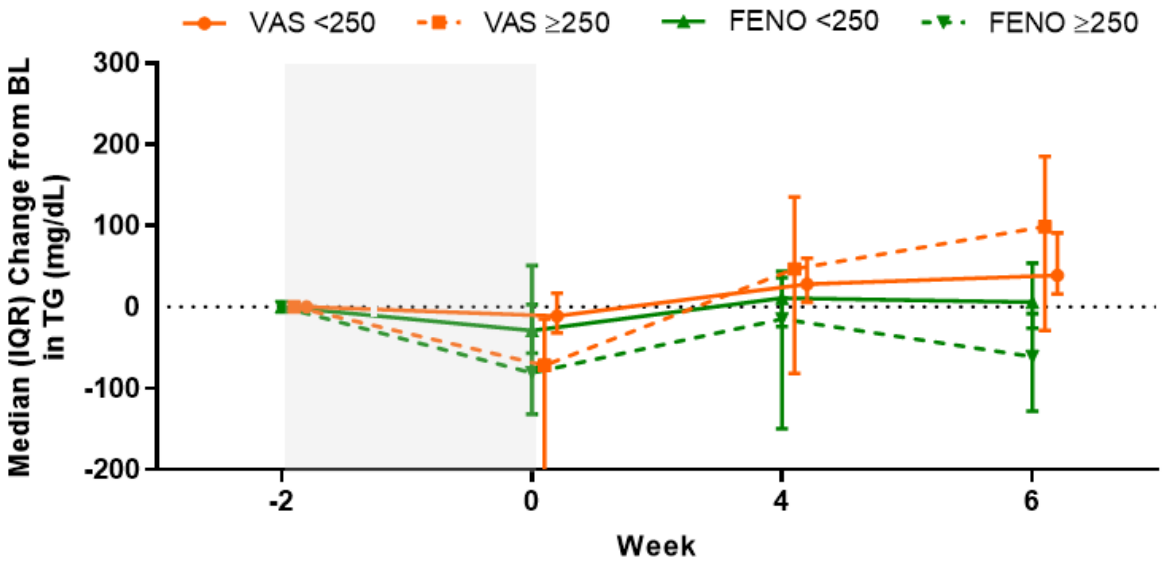
Figure 1. Study GS-US-384-3914 (Cohorts 12 and 13): Median Change From Baseline in Triglycerides by Visit and Treatment (VAS Versus FENO)



Shaded area indicates 2-week pre-treatment period with VAS or FENO monotherapy. CILO+FIR added to VAS or FENO between Weeks 0 and 6.
* p<0.05 vs BL by Wilcoxon signed-rank test.

BL = baseline; CILO = cilofexor (GS-9674); FENO = fenofibrate; FIR = firsocostat (GS-0976); IQR = interquartile range; TG = triglyceride; VAS = icosapent ethyl (Vascepa®)

Figure 2. **Study GS-US-384-3914 (Cohorts 12 and 13): Median Change From Baseline in Triglycerides by Visit, Treatment (VAS Versus FENO), and Pretreatment Baseline Triglyceride Level**



Shaded area indicates 2-week pre-treatment period with VAS or FENO monotherapy.
CILO+FIR added to VAS or FENO between Weeks 0 and 6.
* p<0.05 vs BL by Wilcoxon signed-rank test.

BL = baseline; CILO = cilofexor (GS-9674); FENO = fenofibrate; FIR = firsocostat (GS-0976); IQR = interquartile range; TG = triglyceride; VAS = icosapent ethyl (Vascepa®)

During combination therapy, treatment-emergent Grade 3 triglyceride elevations (500-1000 mg/dL) were observed in 2 participants in each group, all with baseline triglycerides ≥ 250 mg/dL. No Grade 3 or 4 triglyceride elevations were observed in participants with pretreatment triglycerides < 250 mg/dL. Combinations were otherwise safe and well tolerated. The majority of AEs were Grade 1 or Grade 2 and there were no discontinuations due to AEs. No pruritus was reported in either cohort. Overall, 2 SAEs were reported, including 1 participant with Grade 1 noncardiac chest pain in the VAS group and 1 participant with Grade 3 appendicitis in the FENO group which occurred 9 days after the last dose of study drug. Neither SAE was attributed to study drug by the investigator. No deaths were reported. Prior to initiating CILO+FIR, 1 participant in the VAS group with baseline triglycerides of 2.540 mg/dL discontinued VAS after 8 days due to a persistent triglyceride elevation > 500 mg/dL.

1.5.2.2. Study GS-US-454-4378 (ATLAS)

Study GS-US-454-4378 was a global, multicenter, randomized, placebo-controlled, Phase 2b study designed to evaluate the safety and efficacy of SEL, FIR, and CILO as monotherapies and in 2-drug combinations in participants with biopsy confirmed NASH and either bridging (F3) fibrosis or compensated cirrhosis (F4). Participants were randomized to 1 of 7 treatment groups: placebo, SEL 18 mg, CILO 30 mg, FIR 20 mg, SEL 18 mg + CILO 30 mg, SEL 18 mg + FIR

20 mg, or CILO 30 mg + FIR 20 mg. Study drug was administered orally once daily for 48 weeks. Of note, Phase 3 studies evaluating SEL as monotherapy in participants with advanced fibrosis due to NASH demonstrated lack of efficacy of SEL and led to sponsor discontinuation of the SEL monotherapy group in this study.

1.5.2.2.1. Participant Disposition and Demographics

A total of 395 participants were randomized, 392 of which received at least 1 dose of study drug. Across all treatment groups, the majority of participants were female (64.5%) with a median (Q1, Q3) age of 60 (54, 66) years, and 71.9% had type 2 diabetes. The majority of participants had NASH Clinical Research Network (CRN) fibrosis stage F4 (56.4%) and NAS ≥ 6 (56.1%) at baseline. The percentage of participants with NAS ≥ 5 at baseline was 83.1%, including 86% with Grade 2 ballooning and 62% with Grade 3 lobular inflammation.

A total of 317 participants (80.9%) completed study drug and 75 participants (19.1%) prematurely discontinued study drug. Across all groups, the most common reason for study drug discontinuation was sponsor discontinuation of the SEL monotherapy group (8%, 33 participants).

1.5.2.2.2. Safety Results

Overall, treatment with SEL, FIR, and CILO as single agents and 2-drug combinations for 48 weeks was generally well tolerated. The 3 most commonly reported AEs across treatment groups were pruritus, upper respiratory tract infection, and nausea. In the CILO+FIR group, the 3 most commonly reported AEs were pruritus, headache, and diarrhea. Most AEs were Grade 1 or 2 in severity. The incidence of AEs leading to study drug discontinuation was consistent across groups, and ranged from 2.5% to 5.1%, including 3.8% in the CILO+FIR group and 2.6% in the placebo group.

No specific trends in the frequency of Grade 3 or higher AEs were identified across treatment groups. The only Grade 3 or higher AE reported for > 1 participant in any treatment group was Grade 3 cellulitis. Across all groups, 45 participants (11.5%) had an SAE, including 8 participants (10.3%) in the CILO+FIR group. The only SAE reported for > 1 participant was acute myocardial infarction (reported for 1 participant each in the FIR and CILO+FIR groups) and cellulitis. Only 1 participant (CILO+FIR group) had an SAE considered treatment related by the investigator (gastritis), which resolved within 3 days of onset and did not result in study drug discontinuation. Overall, no specific trends in type or onset of SAEs were observed. One death (CILO+SEL; due to cardiac arrest) was reported during the study that was not considered treatment related by the investigator.

Pruritus AEs were reported in 20% to 29% of all participants who received CILO alone or in combination versus 15% who received placebo; most (83%) were mild. In the CILO+FIR group, Grade 1 or 2 pruritus was reported in 28% of participants (16 of 22 cases Grade 1); there were no Grade 3 AEs or discontinuations due to pruritus.

Most laboratory abnormalities were Grade 1 or 2. Overall, the most common Grade 3 or 4 laboratory abnormality was increased triglycerides (hypertriglyceridemia; 3.6%, 14 of 392 participants; 4% to 8% in participants treated with FIR vs 0% to 5% in participants not treated with FIR). The highest abnormality grade of hypertriglyceridemia was Grade 3. All 14 participants with Grade 3 hypertriglyceridemia had Grade 1 or 2 elevated triglycerides at baseline, and for the majority of participants, the Grade 3 elevations decreased in severity to Grade 1 or 2 by Week 48. From baseline to Week 48, the least-squares mean (LSM) changes in triglycerides in participants treated with CILO+FIR was +44 mg/dL compared with 0 mg/dL in the placebo group.

Adverse events of Grade 1 or 2 hypertriglyceridemia were reported for 4 of the 14 participants with Grade 3 or 4 triglycerides, none of which led to study drug discontinuation. Two participants in the CILO+FIR group had Grade 3 ALT abnormalities, with 1 attributed to a concomitant medication (amoxicillin/clavulanic acid), and the other occurring 29 days after discontinuing study medication and 2 days after a repeat liver biopsy. There was no evidence of drug-induced liver injury (DILI) attributable to study medication in the study.

Compared with placebo, CILO+FIR was associated with increases from baseline to Week 48 in total cholesterol (LSM +17 mg/dL [95% CI: 5%-28%]; $P = 0.0050$) and VLDL (+8 mg/dL [95% CI: 4%-12%]; $P < 0.0001$), and reduced HDL(−4 mg/dL [95% CI: −7% to 1%]; $P = 0.0121$); changes in LDL cholesterol were not statistically significant (+9 mg/dL [95% CI: −1% to 18%]; $P = 0.0795$).

1.5.2.2.3. Efficacy Results

The primary histologic endpoint at Week 48 was the proportion of participants who achieved ≥ 1-stage improvement in fibrosis without worsening of NASH (defined as ≥ 1-grade increase from baseline in hepatocellular ballooning or lobular inflammation). The proportion of participants who met the primary histologic endpoint ranged from 11.8% to 20.9% in the active treatment groups compared with 10.5% in the placebo group. In all participants, the highest response rate was observed in the CILO+FIR group (20.9% [14 of 67 participants]; difference from placebo: 10.8%, $P = 0.1658$). Furthermore, in participants with cirrhosis (F4) at baseline, the highest response rate was observed in the CILO+FIR group (33.3% [12 of 36 participants]), a difference of 19.3% versus placebo (14.3% [3 of 21 participants]).

NAS-related histologic endpoints at Week 48 included ≥ 2-point improvement in NAS, ≥ 1-grade improvement in NAS hepatic steatosis, lobular inflammation, and hepatocellular ballooning, and NASH resolution without worsening of fibrosis. In the overall population, the proportion of participants with ≥ 2-point improvement in NAS ranged from 9.0% to 35.3% in the active treatment groups versus 10.5% in the placebo group. The highest response rate was observed in the CILO+FIR group, which was significantly higher compared with placebo (35.3% [24 of 68 participants]; difference from placebo: 25.5%; $P = 0.0016$). The combination of CILO+FIR also led to statistically significant increases in the proportions of participants with a ≥ 1-grade reduction in steatosis (25.8% vs 5.9%, $P = 0.0085$), lobular inflammation (57.4% vs 28.9%, $P = 0.0036$), and ballooning (29.4% vs 13.2%, $P = 0.0433$). The CILO+FIR group had the highest proportion of participants who achieved NASH resolution without worsening of fibrosis (4.5% [3 of 67 participants] vs 0% [0 of 38 participants] with placebo; $P = 0.3454$).

The CILO+FIR group also had significant improvements in ALT (LSM change at Week 48: −18 U/L, $P = 0.0333$ vs placebo), AST (−12 U/L, $P = 0.0497$), cytokeratin 18 M30 fraction (CK18 M30) (−158 U/L, $P = 0.0064$), and estimated glomerular filtration rate (eGFR; 4.5 mL/min, $P = 0.0286$) compared with placebo. Additionally, CILO+FIR led to a larger reduction in total bile acids (−2.7 µmol/L) compared with placebo ($P = 0.0047$), as well as with either CILO or FIR monotherapy.

1.5.2.2.4. Pharmacokinetic Results

Single PK samples were collected from all participants at each study visit CCI [redacted] Using these PK data as well as intensive PK data in healthy participants, a preliminary population PK model was developed to describe the steady-state exposure of CILO, CILO metabolites GS-716070 and GS-1056756, FIR, and FIR metabolite GS-8343773 in participants with NASH. A previous Phase 1 study showed that CILO has no effect on the PK of FIR and, similarly, FIR had no effect on the PK of CILO (Study GS-US-402-2101). Plasma exposures of CILO and its metabolites (GS-716070 and GS-1056756) and FIR and its metabolite (GS-834773) were similar across the applicable single-agent or combination treatment groups. Mean exposures of CILO and GS-716070 were moderately higher in participants with NASH who received CILO 30 mg without regard to food (GS-US-454-4378) compared with participants with NASH who received CILO 30 mg with food in a prior Phase 2 study (GS-US-402-1852). The higher mean exposure following administration of CILO without regard to food is expected given the known food effect. Additionally, modifications were made to the CILO tablet formulation to reduce PK variability, which may have also contributed to differences in CILO PK between the 2 prior studies as described in IB. Mean FIR exposures were consistent with those observed in previous Phase 2 studies (GS-US-384-3914 and GS-US-426-3989).

1.5.3. Clinical Studies Including CILO, FIR, and SEMA

1.5.3.1. Study GS-US-454-5533

Study GS-US-454-5533 was a randomized, open-label, proof-of-concept Phase 2 study that evaluated the safety, tolerability, and efficacy of SEMA administered as monotherapy and in combination with FIR, and/or CILO for 24 weeks in 108 participants with mild to moderate fibrosis due to NASH. Participants were randomized equally to 1 of 5 treatment groups: SEMA monotherapy, SEMA + FIR 20 mg once daily, SEMA + CILO 30 mg once daily, SEMA + CILO 100 mg once daily, and SEMA + FIR 20 mg once daily + CILO 30 mg once daily. In all groups, SEMA was administered SC once weekly with dose escalation from 0.24 mg to a 2.4 mg weekly target dose over the first 16 weeks. The primary objective of the study was to evaluate the safety and tolerability of the study drugs in participants with NASH. CCI [redacted]

1.5.3.1.1. Participant Disposition and Demographics

A total of 108 participants were randomized, all of whom received at least 1 dose of study drug. Across all treatment groups, a majority of participants were female (68.5%), White (85.2%), with a median (Q1, Q3) age of 54 (48, 61) years. The majority of participants (54.6%) had type 2 diabetes and median (Q1, Q3) BMI was 34.3 (30.9, 39.4) kg/m^2. In the overall population, noninvasive tests of liver fibrosis and steatosis were consistent with mild to moderate fibrosis due to NASH, including median (Q1, Q3) ELF of 9.38 (8.91, 9.92), liver stiffness by transient elastography of 9.25 kPa (7.70, 12.00), and MRI-PDFF of 17.87% (11.97, 24.29).

Overall, 92 participants (85.2%), completed study drug. Reasons for discontinuation of study drug included AEs (8 participants, 7.4%), participant decision (6 participants, 5.6%), and lost to follow-up (2 participants, 1.9%).

1.5.3.1.2. Safety Results

Overall, treatment with SEMA as monotherapy or in combination with FIR and/or CILO, for 24 weeks, was generally well tolerated. The tolerability of SEMA in combination with FIR and/or CILO was similar to that of SEMA monotherapy.

Across the treatment groups, the most commonly reported AEs were GI. The most commonly reported AEs by preferred term (PT) were nausea, diarrhea, constipation, and decreased appetite. The incidence of pruritus was low (4.6%); all events occurred in the treatment groups containing CILO, were Grade 1 in severity, and none led to discontinuation of study drug. The incidence of hypoglycemic episodes was also low (4.6%) with all events being Grade 1 or Grade 2 in severity, the majority of which (8/10) were assessed by the investigator as related to study drug.

Five participants (4.6%) had a total of 7 Grade 3 AEs. Of these, 2 participants (1.9%) had 4 Grade 3 AEs assessed by the investigator as related to study drug. One participant in the SEMA monotherapy group had 3 Grade 3 treatment-related AEs of diarrhea, vomiting, and dehydration, and 1 participant in the SEMA + CILO 100 mg group had a Grade 3 treatment-related AE of pancreatitis. The Grade 3 treatment-related AEs of diarrhea, vomiting, and pancreatitis were the only SAEs reported.

Across treatment groups, the AEs leading to discontinuation of study drug were predominantly GI events. The incidence of AEs leading to discontinuation of study drug in the combination groups (range: 4.5% to 9.1%) was no higher than that reported for the SEMA monotherapy group (14.3%). There were no deaths, no pregnancies, and no AEs related to the pen injector device used for SEMA administration. No neoplasms, benign or malignant, were reported.

Overall, 3 participants (2.8%) had Grade 3 or 4 laboratory abnormalities. One participant in the SEMA + FIR 20 mg group, who had a Grade 2 elevation in triglycerides at baseline, had Grade 3 hypertriglyceridemia at Week 4, after which the participant remained on study drug with no further Grade 3 or 4 triglyceride elevations. Two participants in the SEMA+CILO 100 mg group had Grade 4 increases in creatine phosphokinase (CPK), both reported as unrelated by the investigator. For both participants, CPK values returned to baseline levels and there were no further elevations with continued administration of study drug. There was no evidence of hepatotoxicity attributable to study drug.

A dose-dependent increase in fasting LDL cholesterol level was observed with CILO treatment with median changes from baseline to Week 24 of 0 to +13 mg/dL for the 2 treatment groups containing CILO 30 mg and +18 mg/dL in the SEMA + CILO 100 mg group.

Mild increases from baseline to Week 24 in fasting triglycerides were observed for the 2 treatment groups containing FIR. The median increase from baseline to Week 24 in fasting triglycerides was lower for the SEMA + FIR 20 mg + CILO 30 mg group (10 mg/dL) compared with the SEMA + FIR 20 mg group (22 mg/dL).

1.5.3.1.3. Efficacy Results

Compared with SEMA monotherapy, treatment with combinations led to greater reductions from baseline in liver steatosis, as measured by MRI-PDFF and controlled attenuation parameter (CAP). The greatest median reductions from baseline in these parameters were observed for the SEMA + FIR 20 mg + CILO 30 mg group and SEMA + FIR 20 mg group, respectively. Furthermore, the proportion of participants who achieved a $\geq$ 5% absolute reduction in MRI-PDFF at Week 24 was higher in the 4 combination treatment groups (range: 76.5% to 94.4%) compared with the SEMA monotherapy group (64.7%). A similar proportion of participants in all treatment groups achieved a $\geq$ 30% relative reduction in MRI-PDFF at Week 24 (range: 76.5% to 90.5%).

Reductions in liver stiffness as measured by transient elastography at Week 24, were similar or greater in the combination treatment groups as compared with the SEMA monotherapy group, with the greatest median reductions from baseline to Week 24 observed in the 2 treatment groups containing FIR. The proportion of participants with a $\geq$ 25% relative reduction in liver stiffness at Week 24, were 1.4- to 1.7-fold higher in the 4 combination treatment groups (50% to 60%) compared with the SEMA monotherapy group (35.7%).

Treatment with combinations led to improvements in liver enzymes, including ALT and AST, that were similar to or greater than those observed with SEMA monotherapy.

Reductions from baseline to Week 24 in ELF score were observed in all treatment groups, however no significant differences were observed between groups. Further, reductions from baseline in hepatocellular apoptosis (as measured by serum CK18 M30) and inflammation (as measured by serum CRP) were observed in all treatment groups.

At Week 24, similar relative reductions from baseline in body weight and BMI were observed across groups, including SEMA monotherapy and combinations. Overall, glycemic control was similarly improved in all groups, as reflected by median reductions from baseline to Week 24 in HbA_{1c} (range: 0.6% to 1.0%), with greater reductions observed in participants with type 2 diabetes.

1.5.3.1.4. Pharmacokinetic Results

A single PK blood sample was collected from all participants at any time during the study visits at Weeks 1, 4, 8, and 12. The plasma concentrations of FIR, CILO, and their respective metabolites were consistent with those observed in the previous NASH Phase 2 ATLAS study (GS-US-454-4378). These results suggest that the PK of FIR and CILO was not impacted when administered in combination with SEMA.

1.6. Rationale for This Study

Among patients with NASH, those with cirrhosis are at the highest risk of liver-related morbidity and mortality, including progression to end-stage liver disease and HCC. Currently, there are no approved therapies for this patient population. Additionally, fibrosis stage is the primary determinant of overall and liver-related mortality, as well as liver-related morbidity in NASH {Angulo 2015, Ekstedt 2015, Yeh 2014}. Given the complex pathophysiology of NASH, combination regimens may offer superior efficacy compared with monotherapies, both on liver histology and other clinically relevant hepatic and metabolic parameters in this patient population.

Semaglutide is a GLP-1 RA with multiple established beneficial effects, including weight loss, improvements in insulin sensitivity, and a reduction in cardiovascular risk in high-risk patients with type 2 diabetes {Marso 2016}. In a Phase 2 study in participants with NASH and F2-F3 fibrosis, treatment with 0.4 mg SEMA once daily (considered equivalent to a weekly SEMA dose of 2.4 mg), resulted in a significantly higher proportion of participants achieving NASH resolution without worsening of fibrosis compared with placebo at Week 72 (59% vs 17%, $P < 0.001$). In this treatment group, a greater proportion of participants achieved fibrosis improvement ≥ 1-stage without worsening of NASH, however the difference was not significantly greater than with placebo (43% vs 33%, $P = 0.48$). Semaglutide also reduced body weight, with the greatest reduction versus placebo at Week 72 observed in the SEMA 0.4 mg group (−12.5% vs −0.6%). Additionally, compared with placebo, participants treated with SEMA had improvements in liver enzymes (eg, ALT, AST), and markers of hepatocellular injury, apoptosis, and fibrosis (eg, CK18 M30 and M65, ELF score, and liver stiffness by FibroScan) at Week 72. In a Phase 2 study in participants with cirrhosis due to NASH, a 2.4 mg weekly dose of SEMA by subcutaneous injection for 48 weeks was well tolerated but did not demonstrate efficacy as a monotherapy by NASH resolution or fibrosis improvement {Loomba 2023}.

Cilofexor is a nonsteroidal FXR agonist that functions primarily in the small intestine to induce release of FGF19, which suppresses bile acid synthesis, lipogenesis, and gluconeogenesis. In a Phase 2 study, treatment with CILO alone for 24 weeks reduced hepatic steatosis and serum bile

acids in participants with NASH and mild to moderate fibrosis {Patel 2020}. Firsocostat is a liver-targeted, small molecule allosteric inhibitor of ACC that catalyzes the rate-limiting step in DNL and regulates β-oxidation of fatty acids. In a Phase 2 study, treatment with FIR alone for 12 weeks reduced hepatic steatosis, liver biochemistry, and serum fibrosis markers in NASH participants with mild to moderate fibrosis {Loomba 2018}. In a subsequent Phase 2 study (GS-US-454-4378) in participants with advanced fibrosis due to NASH (56% with cirrhosis), the safety and efficacy of CILO and FIR as monotherapies, or in combination (CILO+FIR) for 48 weeks, was evaluated. Among all 7 treatment groups in this study, the largest proportion of participants meeting the primary endpoint of ≥ 1-stage improvement in fibrosis without worsening of NASH was observed in the CILO+FIR group (20.9% vs 10.5% in placebo, $P = 0.1658$). Furthermore, significant improvement in NASH activity based on NAS components of steatosis, lobular inflammation, and hepatocellular ballooning were observed in the CILO+FIR group (all $P < 0.05$ vs placebo) and improvements in liver biochemistry (ALT, AST, total bilirubin), markers of fibrosis (ELF, liver stiffness by FibroScan), and other biomarkers (total bile acids, CK18, insulin, eGFR) were observed. The combination of CILO+FIR was well tolerated in these participants with advanced fibrosis. While the most common AE was pruritus (28% of CILO+FIR participants vs 15% of placebo participants), most cases were mild (83% Grade 1), and no participants discontinued study drug due to pruritus. Over 48 weeks, treatment with CILO+FIR was associated with increases in triglycerides, total and VLDL cholesterol, and reduced HDL cholesterol.

In a subsequent Phase 2 study (GS-US-454-5533), the safety and tolerability of combinations of SEMA, CILO, and/or FIR were evaluated in participants with mild to moderate fibrosis due to NASH over 24 weeks. Treatment with SEMA in combination with FIR 20 mg and CILO 30 mg was generally well tolerated. The most commonly reported AEs were GI, and similar rates of study drug discontinuation due to AEs were observed with combination therapies compared with SEMA monotherapy. Low rates of pruritus in groups administered CILO was observed, including 2 of 21 participants (9.5%) in the SEMA + CILO 30 mg + FIR 20 mg group. In combination treatment groups including CILO 30 mg, median change from baseline to Week 24 in fasting LDL cholesterol was 0 to 13 mg/dL (SEMA + CILO 30 mg and SEMA + FIR 20 mg and CILO 30 mg, respectively). The addition of SEMA to FIR 20 mg partially mitigated FIR-induced triglyceride elevations as compared with observations in prior studies {Loomba 2018}, with a 10 to 22 mg/dL increase in triglycerides observed in the groups administered FIR 20 mg[redacted]

Given that patients with cirrhosis due to NASH have the highest risk of liver-related complications, and that no therapies have been approved for their treatment, this patient population has a high unmet medical need. In light of the complex pathophysiology of NASH, the potential of weight loss to drive histologic improvement, and the relevance of long-term cardiovascular risk in NASH patients, combination regimens including a GLP-1 RA with liver-targeted therapies (such as CILO and FIR) offer the potential for greater overall efficacy than a monotherapy approach. To evaluate the histologic benefits of SEMA, CILO/FIR, and their combination in participants with cirrhosis due to NASH, this Phase 2 study has been designed as

an international, multicenter, randomized, double-blind, double-dummy, placebo-controlled study to evaluate the safety and efficacy of these treatments over 72 weeks. In total, approximately 440 participants with histologically confirmed, compensated cirrhosis due to NASH (F4 fibrosis by the NASH CRN classification) will be enrolled. Participants will be randomized in a 3:3:3:2 ratio to receive SEMA+CILO/FIR, CILO/FIR, SEMA, or PTM for 72 weeks. Given the beneficial effects of SEMA on NASH resolution and metabolic parameters (body weight, glucose, lipids) in participants with F2-F3 fibrosis (Study NN9931-4296), as well as improvements in fibrosis and necroinflammatory activity with the combination of CILO+FIR in participants with F3-F4 fibrosis (Study GS-US-454-4378), it is hypothesized that a combination of SEMA+CILO/FIR will have additive benefits, leading to both NASH resolution and fibrosis improvement in NASH patients with cirrhosis. Considering the metabolic benefits of SEMA, including weight loss and improvements in lipids, the addition of SEMA to CILO/FIR is also hypothesized to mitigate elevations in serum lipids that have been observed with CILO/FIR treatment in prior studies.

The primary objective of this study is to evaluate whether the combination of SEMA with CILO/FIR causes fibrosis regression in this high-risk patient population. Efficacy will be determined based on changes in liver histology, with the primary efficacy endpoint of ≥ 1-stage improvement in fibrosis without worsening of NASH on liver biopsy at Week 72. Given the limitations of conventional histological assessment of liver biopsies, including the potential for sampling error, variability in pathological interpretation, and limited sensitivity for detection of treatment effects due to the ordinal nature of current classification systems, multiple noninvasive markers of fibrosis (ELF, liver stiffness by FibroScan), and automated, quantitative machine learning-based methods of histologic assessment will also be evaluated in this study.

1.7. Rationale for Dose Selection of Semaglutide

The proposed target dose of SEMA 2.4 mg once weekly is based on an integrated evaluation of efficacy and safety as well as on exposure (C_{avg} and C_{max}). Results from the Phase 2 dose-finding study (NN9536-4153) in participants with obesity showed that the SEMA 0.4 mg once-daily dose led to the greatest effect on weight loss while displaying an acceptable tolerability profile. Furthermore, data from the SEMA SC type 2 diabetes development program (SUSTAIN studies with once-weekly dosing and Study NN9535-4191 with once-daily SC dosing of up to 0.3 mg/day) did not support the hypothesis that once-daily dosing provides better GI tolerability as compared with once-weekly dosing.

Based on population PK modeling, it was estimated that a once-weekly maintenance dose of SEMA 2.4 mg would result in similar C_{max} at steady state as that obtained by the once-daily 0.4 mg SEMA dose in the Phase 2 dose-finding Study NN9536-4153. When comparing the simulated human exposure at 2.4 mg weekly to the animal exposures at the NOAEL, exposure ratios are above 1, indicating that exposure at 2.4 mg weekly is supported by nonclinical studies. Based on these data, a maintenance dose of SEMA 2.4 mg once weekly was chosen for the Phase 3 weight management and NASH development programs. Based on experience from the SEMA type 2 diabetes and weight management development program, a similar fixed-dose escalation regimen was selected, with dose escalation every 4 weeks until the target dose of 2.4 mg is reached after 16 weeks.

1.8. Rationale for Dose Selection of CILO and FIR in Fixed-Dose Combination ± SEMA

The doses of CILO and FIR for evaluation in this study, 30 mg and 20 mg once daily, respectively, are supported by a combination of safety and efficacy data from Phase 1 and 2 studies in healthy participants and participants with NASH as summarized below. Regarding combination dosing, available PK and safety data from Study GS-US-454-4378 in participants with advanced fibrosis due to NASH demonstrated no clinically meaningful changes in CILO and FIR exposure, or the safety profile of the individual therapies, when coadministered. Pharmacokinetic and safety data from Study GS-US-454-5533 in participants with mild to moderate fibrosis due to NASH demonstrated no clinically meaningful changes in CILO and FIR exposures or the safety profile of the individual therapies when administered in combination with SEMA.

A CILO dose of 30 mg once daily is supported by PK, PD, safety, and efficacy data from Phase 1 studies in healthy participants and participants with hepatic impairment (Studies GS-US-402-1851, GS-US-454-4315, GS-US-402-3885), and participants with advanced fibrosis due to NASH (Studies GS-US-384-3914, GS-US-454-4378). In PD studies, CILO doses ≥ 30 mg daily provided comparable intestinal FXR agonism as assessed by increases in FGF19 exposure, including in participants with advanced fibrosis due to NASH. In a Phase 2 dose-ranging study (GS-US-402-1852) in NASH participants with mild to moderate fibrosis, CILO 30 mg and 100 mg administered once daily for 24 weeks showed dose- and exposure-dependent reductions in MRI-PDFF and liver biochemistry. At the 100-mg dose, an increased incidence of Grade 2 or 3 pruritus (14.3% vs 1.8% with 30 mg), as well as greater increases in LDL cholesterol (LSM change from baseline to Week 24: +7 mg/dL with 100 mg vs 0 mg/mL with 30 mg) were observed. In the ATLAS study (GS-US-454-4378), which evaluated an optimized formulation of CILO 30 mg that would approximate exposures of 60 mg with the formulation used in Study GS-US-402-1852, the incidence of pruritus in participants treated with CILO was low and no pruritus-related treatment discontinuations in participants treated with CILO+FIR were observed. Moreover, CILO treatment was associated with improvements in hepatic fat, liver biochemistry, and liver stiffness by transient elastography. The data described above suggest that a 30 mg dose of CILO with the optimized formulation poses a relatively minimal risk for pruritus, which is dose-dependent, and is expected to have a lower risk of pruritus-related treatment discontinuation and elevations in LDL cholesterol than higher doses, while still providing adequate FXR activation to contribute to improvements in fibrosis and other NASH-related parameters when used in combination with FIR. While exposures of CILO are increased in mild hepatic impairment (1.8-fold), preliminary population PK data from Study GS-US-454-4378 indicate no difference in CILO exposures in participants with F3 or F4 fibrosis. Additionally, CILO 30 mg was well tolerated over 12 and 48 weeks in participants with compensated cirrhosis due to NASH (Studies GS-US-384-3914, GS-US-454-4378). Data from the Phase 1 Study GS-US-402-3885 indicated that CILO and metabolite exposures increase significantly in participants with moderate Child-Pugh (CP) Class B and severe (CP Class C) hepatic impairment. These data support an approach wherein no CILO dose adjustment is required for participants with CP Class A cirrhosis; however, participants with clinical or biochemical (ie, CP Class B or C) evidence of hepatic decompensation will not be eligible for this study.

A FIR dose of 20 mg once daily is supported by the safety, tolerability, and effects of FIR on DNL from Studies 0976-101, 0976-102, and 0976-103 as described in the FIR IB, and the safety and efficacy observed in participants with mild hepatic impairment (Study GS-US-426-3988) and NASH (Studies GS-US-426-3989, GS-US-384-3914, GS-US-454-4378). In the Phase 2 Study GS-US-426-3989, FIR 5 mg and 20 mg doses were evaluated for 12 weeks in participants with mild to moderate fibrosis due to NASH. Both dose levels demonstrated similar safety profiles, but only the 20 mg dose showed statistically and clinically significant reductions in hepatic steatosis measured by MRI-PDFF. Firsocostat 20 mg also resulted in larger reductions in liver biochemistry (ie, ALT) and serum markers of fibrosis (ie, tissue inhibitor of metalloproteinase 1 and procollagen III amino terminal peptide). These data were consistent with reductions in liver biochemistry and serum markers of fibrosis observed in participants treated with FIR 20 mg alone in Study GS-US-454-4378. In this study, there were no meaningful differences in FIR exposures in participants with F4 and less than F4 fibrosis, or between participants who experienced AEs or laboratory abnormalities and those that did not. Based on these data, FIR exposures in participants with mild hepatic impairment (CP Class A) are expected to remain ≥ 22- and ≥ 105-fold lower than the FIR exposures observed at the NOAELs in the 39-week dog and 26-week rat toxicity studies, respectively. Based on PK data in participants with mild hepatic impairment and the overall safety profile of FIR, dose adjustments are not considered necessary for participants with compensated cirrhosis.

1.9. Benefit-Risk Assessment for the Study

This study will provide information regarding the safety and efficacy of SEMA, CILO/FIR, and their combination in patients with compensated cirrhosis due to NASH. The potential benefits of SEMA as a monotherapy in participants with F2-F3 fibrosis due to NASH were demonstrated in the Phase 2 study (NN9931-4296). As described above, compared with placebo, SEMA led to the highest proportion of participants achieving NASH resolution without worsening of fibrosis, improvements in liver biochemistries, markers of liver fibrosis, body weight, glycemic control, and lipid parameters at Week 72. In participants with F4 fibrosis due to NASH, SEMA as a monotherapy in the Phase 2 study (NN9931-4492) failed to promote fibrosis improvement or NASH resolution at Week 48. However, participants receiving SEMA experienced greater improvements in liver steatosis by MRI-PDFF, change in ALT concentration, decreased bodyweight, reductions in HbA1c, triglycerides, and VLDL. The potential benefits of CILO and FIR in combination were demonstrated in a Phase 2 study (GS-US-454-4378) in participants with advanced fibrosis, including 56% with compensated cirrhosis (F4). As described above, CILO+FIR led to the highest proportion of participants achieving fibrosis regression without worsening of NASH after 48 weeks of treatment, and, compared with monotherapy or placebo, led to greater improvements in NAS parameters, liver biochemistry, markers of fibrosis (ELF, liver stiffness by FibroScan), and other relevant biomarkers (CK18 M30 and M65, total bile acids, insulin). Based on the above, as well as data from the Phase 2 Study GS-US-454-5533, which demonstrated that combinations, including SEMA+CILO+FIR, led to greater reductions in liver steatosis (MRI-PDFF, CAP), liver biochemistries (ALT, AST), and additional biomarkers (CK18 M30, FGF-21) compared with monotherapy, it is hypothesized that the combination of SEMA+CILO/FIR will translate to greater histologic and metabolic benefits in this patient population. Participants randomized to the placebo control group in this study may

benefit from frequent medical monitoring and close assessment of their NASH and associated pathologies during the duration of placebo treatment (eg, surveillance for HCC and management of cardiovascular risk).

Potential risks of this study include the limited number of participants with cirrhosis due to NASH, as compared with those with noncirrhotic (F1-F3) NASH, in which SEMA's safety and efficacy has been evaluated. In noncirrhotic NASH, SEMA was well tolerated over 72 weeks in a Phase 2 study (NN9931-4296) and in cirrhotic participants with NASH over 48 weeks in a Phase 2 study (NN9931-4492) in which there was no increased rate of GI AEs in participants with more versus less advanced fibrosis, and no increased rate of discontinuation due to AEs in the high-dose SEMA arm compared with the placebo arm. The PK of SEMA are similar in cirrhotic and noncirrhotic participants. To mitigate the potential risk of poor tolerability due to GI AEs, with SEMA, participants will be counseled on expected GI AEs during SEMA dose escalation and lifestyle strategies to aid in their mitigation (Section 6.8.12). As the majority of GI AEs attributed to SEMA are experienced during dose escalation, visits are scheduled every 4 weeks through Week 16 to enable close monitoring. In cases of poor tolerability, participants may delay SEMA dose escalation (Section 5.5.2) and, if necessary, remain at a dose lower than the target. Additional safety considerations specific to SEMA include the observation of thyroid C-cell tumors in nonclinical carcinogenicity studies. These rodent C-cell tumors are caused by a nongenotoxic GLP-1 receptor mechanism to which rodents are particularly sensitive. Given that the GLP-1 receptor is not expressed in normal human thyroid and that medullary thyroid carcinoma has not been associated with SEMA in clinical studies, the clinical relevance of this observation is considered low. Nevertheless, participants with a personal or family history of multiple endocrine neoplasia type 2 or medullar thyroid carcinoma will be excluded from this study, and any participants who develop medullary thyroid carcinoma must discontinue study drug. Additional potential risks associated with the GLP-1 RA class, including SEMA, include gallbladder or hepatobiliary events and acute pancreatitis. Given this, participants with a recent history of symptomatic gallbladder or biliary tract disease are excluded, unless a cholecystectomy has been performed, and participants with a history of chronic or recent acute pancreatitis are excluded. Additionally, any participants who develop suspected acute pancreatitis must discontinue study drug (Section 3.5).

An additional risk is the fact that CILO and FIR are new chemical entities studied in a limited number of participants with cirrhosis. However, the combination of CILO+FIR was well tolerated in participants with F3-F4 fibrosis over 48 weeks in the Phase 2 Study GS-US-454-4378. In this study, the AE of pruritus occurred in 28% of participants treated with CILO+FIR versus 15% of participants treated with placebo; however, the majority of cases (83%) were mild (Grade 1) and no participants discontinued due to pruritus. In the Phase 2 Study GS-US-454-5533, which evaluated SEMA in combination with CILO and/or FIR in participants with mild to moderate fibrosis due to NASH, combinations were generally well tolerated, with the most common AEs gastrointestinal in nature and no higher rate of discontinuation due to AE in combination groups versus SEMA alone. Furthermore, pruritus observed exclusively in CILO containing groups was limited, all Grade 1, and no participants discontinued due to pruritus. To mitigate the risk of treatment discontinuation due to pruritus, close monitoring for new or

worsening pruritus will be conducted and a pruritus management plan is included in this protocol (Section 7.7.5).

In the Phase 2 Study GS-US-454-4378, CILO+FIR led to an increase in total and VLDL cholesterol, and a decrease in HDL cholesterol at Week 48. A nonsignificant increase in LDL cholesterol was also observed. Given these changes, as well as the frequency of cardiovascular risk factors in the NASH patient population, the cardiovascular risk profile of participants will be evaluated prior to treatment initiation and on an ongoing basis. Upon treatment initiation, lipids will be closely monitored and guidance has been provided in the protocol for initiation or dose modification of lipid lowering therapies as necessary (Section 7.7.4)

Regarding triglycerides specifically, prior studies of FIR have revealed asymptomatic Grade 3 or 4 elevations in triglycerides that resolved spontaneously or with treatment with fibrates or fish oil. In Study GS-US-426-3988, participants who had abnormal triglycerides at baseline were more likely to be affected. Therefore, participants with baseline triglycerides greater than 250 mg/dL were excluded from the subsequent Phase 2 combination study (GS-US-454-4378). This approach resulted in fewer Grade 3 or 4 triglyceride elevations in participants treated with FIR 20 mg daily. In the current study, participants with serum triglycerides over 250 mg/dL are excluded unless triglycerides can be optimized prior to Day 1 (eg, via conservative or pharmacologic management), per the discretion of the investigator. To mitigate the risks associated with on-treatment triglyceride elevations, lipids will be closely monitored throughout the study, with additional guidance regarding criteria for study drug withholding and initiation of triglyceride management (eg, treatment with fibrates), or study drug discontinuation provided in Section 7.7.4.

An additional risk of this study is the potential for drug-related hepatotoxicity, particularly in participants with underlying cirrhosis. In the Phase 2 combination study (GS-US-454-4378), 2 of 78 participants treated with CILO+FIR experienced an ALT elevation > 5 times the upper limit of normal (ULN). However, 1 case was attributed to a concomitant treatment with amoxicillin/clavulanic acid, a common cause of hepatotoxicity, and the other case was noted 29 days following completion of treatment and 2 days after a liver biopsy which did not suggest DILI. Further, when CILO and/or FIR were evaluated in combination with SEMA in the Phase 2 Study GS-US-454-5533, treatment-emergent elevations in serum ALT were not observed. Nevertheless, in order to mitigate any potential risk of hepatotoxicity, close monitoring of liver biochemistry values will be performed and parameters for discontinuation of study drug, including liver test abnormalities and clinical criteria consistent with hepatic decompensation, have been defined and will be closely followed (Section 7.7.1). Importantly, for any participant who meets criteria for study drug withholding due to concern for DILI, the data monitoring committee (DMC) will be notified and resumption of study drug may only be considered after review of relevant safety data by the DMC.

Additional risks to study participants include those attributable to study participation in general, including risks associated with frequent clinic visits, laboratory blood draws, and liver biopsy, and the potential discomfort associated with these procedures. Strategies to mitigate these risks include close monitoring of laboratory values as well as AEs. Parameters for discontinuation of study drug and/or notification of the DMC due to AEs and nonhepatic laboratory abnormalities are also defined and will be closely followed. Finally, an infectious disease pandemic may pose additional risks to study drug availability, the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Appendix 11.2 provides further details on the relevant risks and risk mitigation strategies.

Overall, the nonclinical and clinical data to date suggest a positive benefit/risk profile in support of further evaluation of SEMA, CILO/FIR, and their combination in participants with compensated cirrhosis due to NASH, a high-risk patient population without any available treatment options. Appropriate safety monitoring will be conducted throughout the study to further characterize the safety profiles of these treatment regimens in this patient population.

1.10. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

A list of study interventions and their marketing authorization status is provided in Appendix 11.3.

Auxiliary medicinal products/noninvestigational medicinal products are not used in this study.

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate whether the combination of SEMA with the FDC of CILO/FIR causes fibrosis improvement (according to the NASH CRN classification) without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation) in participants with compensated cirrhosis due to NASH, as compared with placebo

The secondary objectives of this study are as follows:

- To confirm the contribution of CILO/FIR to fibrosis improvement without worsening of NASH in participants treated with the combination of SEMA and CILO/FIR by comparing with participants treated with SEMA alone
- To evaluate whether the combination of SEMA with the FDC of CILO/FIR causes NASH resolution (defined as lobular inflammation of 0 or 1 and hepatocellular ballooning of 0) in participants with compensated cirrhosis due to NASH, as compared with placebo
- To confirm the contribution of SEMA to NASH resolution in participants treated with the combination of SEMA and CILO/FIR by comparing with participants treated with CILO/FIR alone

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3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is as follows:

- ≥ 1-stage improvement in fibrosis (according to the NASH CRN classification) without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation) at Week 72 in the SEMA+CILO/FIR versus placebo groups

The secondary endpoints of this study are as follows:

- ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 72 in participants treated with SEMA+CILO/FIR versus SEMA alone
- NASH resolution (defined as lobular inflammation of 0 or 1 and hepatocellular ballooning of 0) at Week 72 in the SEMA+CILO/FIR versus placebo groups
- NASH resolution at Week 72 in participants treated with SEMA+CILO/FIR versus CILO/FIR alone

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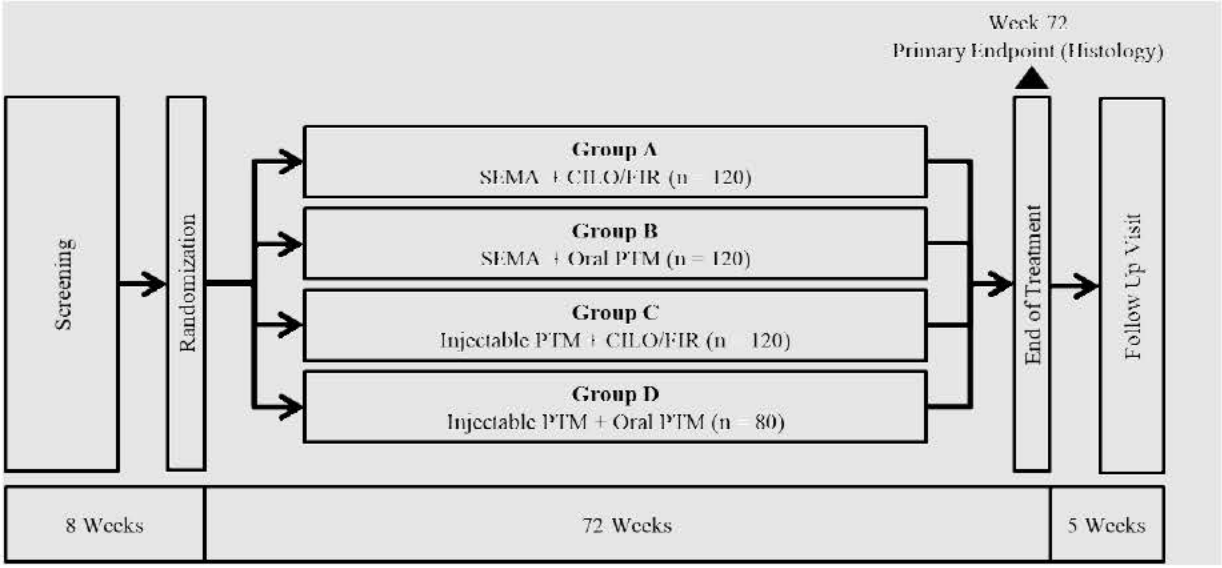
3.2. Study Design

This is a Phase 2, randomized, double-blind, double-dummy, placebo-controlled study evaluating the efficacy and safety of SEMA, CILO/FIR, and their combination in participants with compensated cirrhosis due to NASH.

Participants meeting the study's entry criteria will be randomly assigned in a 3:3:3:2 ratio to 1 of 3 active treatment groups (SEMA+CILO/FIR, SEMA+PTM CILO/FIR, PTM SEMA+CILO/FIR) or placebo (PTM SEMA+PTM CILO/FIR), as shown in Figure 3 below. Randomization will be stratified by the presence or absence of type 2 diabetes as determined by medical history or based on screening laboratory values if previously undiagnosed (ie, HbA_{1c} $\geq$ 6.5% or fasting plasma glucose $\geq$ 126 mg/dL, confirmed on repeat testing), and by ELF score ($\geq$ 11.30 or < 11.30 during screening).

Figure 3. GS-US-454-6075 Study Schema



CILO = cilofexor (GS-9674); FIR = firsocostat (GS-0976); PTM = placebo-to-match; SEMA = semaglutide

3.3. Study Treatments

Participants meeting the study's entry criteria will be randomly assigned in a 3:3:3:2 ratio to 1 of 3 active treatment groups (SEMA+CILO/FIR, SEMA+PTM CILO/FIR, PTM SEMA+CILO/FIR) or placebo group (PTM SEMA + PTM CILO/FIR) as presented in Section 3.2.

Details regarding the dosage forms, packaging, and labeling of SEMA and CILO/FIR are provided in Sections 5.2 and 5.3, respectively.

3.4. Duration of Treatment

Participants will be treated for 72 weeks. Total study duration will be up to 85 weeks, including up to 8 weeks for screening, a 72-week treatment period, and a 5-week follow-up period.

3.4.1. Poststudy Care

If Gilead Sciences (Gilead) discontinues development of the study drug, further provision of study drug to participants may be discontinued, independent of treatment effect. No poststudy treatment will be provided by Gilead or Novo Nordisk for participants in this study. The long-term care of all study participants will remain the responsibility of their primary treating physician.

3.5. Discontinuation Criteria

It is strongly recommended to contact the medical monitor or designee to discuss whether a participant has met criteria for discontinuation of study drugs as soon as possible when any of the following conditions are observed.

Study drugs must be discontinued in the following circumstances:

- Any Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 AE, deemed life threatening and related to study drug(s) in the opinion of the investigator
- Participant progression to decompensated cirrhosis, as defined by any of the following:
  - Grade 2 ascites (symptomatic; medical intervention indicated), graded using the CTCAE Toxicity Grading Scale
  - HE of Grade 2 or above according to the West Haven Criteria (Appendix 11.4) requiring treatment
  - Portal hypertension–related upper GI bleeding identified by endoscopy and requiring hospitalization, including events of bleeding from esophageal varices, gastric varices, and portal hypertensive gastropathy
- CP score > 6 on 2 consecutive occasions, preferably within 72 hours, unless due to an alternative etiology (eg, Gilbert's syndrome or therapeutic anticoagulation) (Section 6.8.5)
- Liver transplantation or qualification for liver transplantation, defined as MELD score > 12 on at least 2 consecutive occasions, preferably within 72 hours, unless due to an alternative etiology (eg, Gilbert's syndrome or therapeutic anticoagulation)
- Diagnosis of HCC or other hepatobiliary cancer
- Fasting serum triglycerides > 1000 mg/dL confirmed on 2 consecutive occasions, preferably within 48 hours
- Fasting serum triglycerides > 500 mg/dL, confirmed on 2 consecutive occasions, preferably within 48 hours, in participants on maximal dose of fibrate in the opinion of the investigator
- Diagnosis of acute pancreatitis, including pancreatitis attributed to elevated serum triglycerides in the opinion of the investigator
- Diagnosis of medullary thyroid carcinoma
- Concomitant treatment with nonprotocol GLP-1 RAs
- Surgical treatment for obesity

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the participant may resume study dosing at the discretion of the investigator

- Unacceptable toxicity (Section 7.7), or toxicity that, in the judgment of the investigator, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest

- Participant request to discontinue for any reason

- Significant participant noncompliance, in the judgment of the investigator

- Significant protocol deviation that impacts participant safety in the opinion of the medical monitor or designee

- Pregnancy during the study (Appendix 11.6)

- Discontinuation of the study at the request of Gilead, regulatory agencies, or an institutional review board (IRB) or independent ethics committee (IEC) or ethics committee (EC)

3.6. End of Study

The end of study is defined as when the last participant enrolled has completed the final visit in the study (including the follow-up visit) or is considered lost to follow-up.

3.7. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, local laboratory(ies), specialty laboratory(ies) (for PK, PD, biomarker, and/or biopsy data), central pathology laboratory, interactive response technology (IRT) system, and/or other vendors as designated by sponsor.

3.8. Biomarker Testing

3.8.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected from all participants who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs), and to better understand the biological pathways of SEMA, CILO, and FIR and how they affect downstream markers of the regulation of these pathways. Biological specimens will also be used to increase the knowledge of diseases such as NASH, liver fibrosis, and inflammatory diseases, and/or the validation of a companion diagnostic for NASH. The specific analyses will include, but will not be limited to, the biomarkers and assays described in Table 1. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens

provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of study to remove tests no longer indicated and/or to add new tests based upon new state of the art knowledge.

Liver tissue, blood, stool, and urine samples will be collected at the time points listed in Appendix 11.5 to measure biomarkers which may include but not be limited to those listed in Table 1. If a test will no longer be performed, sample collection may also be withdrawn to reduce burden on participants.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements.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4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

This study will enroll approximately 440 participants with compensated cirrhosis due to NASH.

4.1.1. Participant Replacement

Participants who discontinue before the end of study will not be replaced.

4.2. Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Men and women between 18 and 80 years of age, inclusive, based on the date of the screening visit

2) Willing and able to give informed consent prior to any study-specific procedures being performed

3) Cirrhosis (F4) due to NASH as defined by 1 of the following:

   a) A historical liver biopsy within 180 days of screening that, in the opinion of the central pathologists, is evaluable and consistent with cirrhosis (F4) and NASH (defined as the presence of steatosis Grade ≥ 1, hepatocellular ballooning Grade ≥ 1, and lobular inflammation Grade ≥ 1, according to NAS)

      OR

   b) In participants without a qualifying historical liver biopsy, if FibroScan ≥ 9.9 kPa at screening, a screening liver biopsy may be performed. The screening liver biopsy must, in the opinion of the central pathologists, be evaluable and meet histologic criteria as specified in inclusion criterion 3a)

      OR

   c) In participants with a historical liver biopsy completed more than 180 days prior to screening that is consistent with cirrhosis (F4) and NASH, as determined by a local reader, a screening liver biopsy may be performed. The screening liver biopsy must, in the opinion of the central pathologists, be evaluable and meet histologic criteria as specified in inclusion criterion 3a)

4) The following laboratory parameters at screening, as determined by the central laboratory:

   a) eGFR ≥ 30 mL/min/1.73m^2, as calculated by the Modification of Diet in Renal Disease (MDRD) equation to estimate CL_{cr}

   b) HbA_{1c} ≤ 10% (or serum fructosamine ≤ 400 µmol/L if HbA_{1c} is not quantifiable)

   c) Hemoglobin > 10.6 g/dL

   d) International normalized ratio (INR) ≤ 1.4, unless due to therapeutic anticoagulation

   e) Total bilirubin ≤ 1.3 × ULN (unless due to an alternative etiology such as Gilbert's syndrome or hemolytic anemia)

   f) Serum albumin ≥ 3.5 g/dL

   g) Serum ALP ≤ 2 × ULN

   h) Platelet count ≥ 125,000/µL

   i) Serum triglyceride level ≤ 250 mg/dL. If initial screening value is > 250 mg/dL, triglycerides may be retested during the screening period. Fasting serum triglycerides must be confirmed to be ≤ 250 mg/dL prior to Day 1. Management of hypertriglyceridemia may be initiated or modified at investigator discretion during the screening period (Section 7.7.4.1)

   j) ALT < 5 × ULN

5) BMI ≥ 23 kg/m^2 at screening

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

1) Any history of decompensated liver disease in the opinion of the investigator, including clinically relevant ascites, HE, or variceal bleeding

2) CP score > 6 at screening, unless due to an alternative etiology such as Gilbert's syndrome or therapeutic anticoagulation

3) MELD score > 12 at screening, unless due to an alternative etiology such as therapeutic anticoagulation

4) Chronic hepatitis B virus (HBV) infection (hepatitis B surface antigen [HBsAg] positive)

5) Chronic hepatitis C virus (HCV) infection (HCV antibody and HCV RNA positive). Participants cured of HCV infection less than 2 years prior to the screening visit are not eligible

6) Other causes of liver disease based on medical history and/or central pathologists' review of liver histology, including but not limited to: alcoholic liver disease, autoimmune disorders (eg, PBC, PSC, autoimmune hepatitis), drug-induced hepatotoxicity, Wilson disease, clinically significant iron overload, or alpha-1-antitrypsin deficiency

7) History of liver transplantation

8) Current or prior history of HCC

9) HIV infection

10) Weight loss > 10% within 180 days of screening, or > 5% between the date of the biopsy used for eligibility and the date of screening

11) Any weight reduction surgery or procedure in the 2 years prior to screening or malabsorptive weight loss surgery (eg, Roux-en-Y or distal gastric bypass) at any time prior to screening

12) History of intestinal resection that could result in malabsorption of study drug

13) Planned coronary, carotid, or peripheral artery intervention or unstable cardiovascular disease in the opinion of the investigator, including any of the following:

    a) Unstable angina, myocardial infarction, coronary artery bypass graft surgery, or coronary angioplasty within 180 days prior to screening

    b) Transient ischemic attack or cerebrovascular accident within 180 days prior to screening

    c) Symptomatic valvular heart disease or hypertrophic cardiomyopathy

    d) Symptomatic congestive heart failure

    e) Uncontrolled or recurrent ventricular tachycardia or arrhythmia requiring an automatic implantable cardioverter defibrillator. Stable, controlled atrial fibrillation is allowed

    f) An emergency room visit or hospitalization for confirmed cardiovascular disease within 180 days prior to screening

14) History of uncontrolled chronic pulmonary disease in the opinion of the investigator (eg, chronic obstructive pulmonary disease, interstitial lung disease) within 180 days prior to screening

15) Men who habitually drink greater than 21 units/week of alcohol or women who habitually drink greater than 14 units/week of alcohol (1 unit is equivalent to 12 oz/360 mL of beer, a 4 oz/120 mL glass of wine, or 1 oz/30 mL of hard liquor)

16) Positive urine drug screen for amphetamines, cocaine, or opiates (eg, heroin, morphine) at screening, unless due to a prescription medication (eg, oxycodone, methylphenidate) and the prescription and diagnosis are reviewed and approved by the investigator. Participants on stable methadone or buprenorphine maintenance treatment for at least 180 days prior to screening may be included in the study

17) Use of any prohibited concomitant medication prior to enrollment as described in Table 4:

    a) Participants on vitamin E regimen ≥ 800 IU/day, or pioglitazone, must be on a stable dose in the opinion of the investigator for at least 180 days prior to the historical or screening liver biopsy

    b) Participants taking antidiabetic medications must be on a stable dose, in the opinion of the investigator, for at least 90 days prior to the historical or screening liver biopsy

18) Participation in another investigational study of a drug or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to the date of screening and through the end of the study. Participation in a study of an investigational device may be approved by the medical monitor or designee

19) History of malignancy within 5 years of screening with the following exceptions:

    a) Adequately treated carcinoma in situ of the cervix

    b) Adequately treated basal or squamous cell cancer or other localized nonmelanoma skin cancer

20) For participants with type 2 diabetes diagnosed prior to the date of the screening visit OR based on screening visit results (HbA_{1c} ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dL, confirmed on repeat testing), participants must have no evidence of uncontrolled and potentially unstable retinopathy or maculopathy as determined by a fundoscopic examination performed starting 90 days prior to screening visit date through Day 1. If there has been worsening of the participant's visual function since a historical fundoscopic examination in the opinion of the investigator, then the fundoscopic examination must be repeated prior to Day 1 for eligibility. Pharmacological pupil dilation is a requirement unless using a digital fundus photography camera specified for nondilated examination.

21) Acute pancreatitis within 180 days prior to screening

22) History or presence of chronic pancreatitis

23) History of symptomatic gallbladder or biliary tract disease in the opinion of the investigator within 6 months prior to screening, unless a cholecystectomy has been performed

24) Presence or history of type 1 diabetes

25) Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullar thyroid carcinoma

26) Treatment with GLP-1 RAs (including SEMA) in the period from 90 days prior to the screening visit and from 90 days prior to the date of the historical qualifying liver biopsy (if applicable)

27) Female who is pregnant, breastfeeding, intends to become pregnant, or is of childbearing potential and not using an adequate contraceptive method as described in Appendix 11.6

28) Men who engage in heterosexual intercourse not using an adequate method of contraception as described in Appendix 11.6

29) Presence of any laboratory abnormality or condition that, in the opinion of the investigator, could interfere with or compromise a participant's treatment, assessment, or compliance with the protocol and/or study procedures. This includes a history of substance abuse and/or psychiatric condition requiring hospitalization and/or emergency room visit within 2 years of screening

30) Known hypersensitivity to the study drug(s), metabolites, or formulation excipient(s)

31) For participants who have not completed a series of an authorized COVID-19 vaccination regimen prior to screening, a positive result for COVID-19 on SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

This is a randomized, double-blind, double-dummy, placebo-controlled study. Participants meeting the study's entry criteria will be randomly assigned in a 3:3:3:2 ratio to 1 of 3 active treatment groups or PTM as described in Section 3.2.

5.1.1. Randomization

An IRT system will be used for centralized randomization, stratification, and treatment assignment. Investigative site personnel will obtain the participant's identification number and study drug assignment from the IRT. Participants and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Randomization will be stratified by the presence or absence of type 2 diabetes as determined by medical history or based on screening laboratory values if previously undiagnosed (ie, $HbA_{1c} \geq 6.5\%$ or fasting plasma glucose ≥ 126 mg/dL, confirmed on repeat testing), and by ELF score (≥ 11.30 or < 11.30 during screening).

5.1.2. Blinding

During the randomized phase, participants and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Study personnel who may be unblinded because of the nature of their functional or study role without additional documentation, as specified in Gilead procedural documents, include the following:

- Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in an IRT for purposes of study drug inventory management
- Individuals in Patient Safety (PS) who review individual case data and/or group-level summaries contained within the safety database when they are involved in activities such as aggregate report generation, signal management, or expedited reporting of suspected unexpected serious adverse reactions (SUSARs)
- Individuals who are involved in bioanalytical/biomarker data transfer and sample/assay review.
  - The Bioanalytical File Administrator in either Bioanalytical Laboratory Clinical Data Management or Biomarker and Bioanalytical Operations who facilitates the transfer of bioanalytical (eg, PK, antidrug antibody) files between Gilead and bioanalytical laboratories
  - Bioanalytical Chemistry scientists who monitor the development, validation, and performance of bioanalytical assays

  - The personnel in bioanalytical laboratories involved in sample receipt, analysis, data review, and data transfer

  - Personnel (eg, Biomarker Sciences) not serving on the study management team who review assay results for samples collected per the study procedures

- Regulatory Quality and Medical Governance personnel in Research and Development (R&D Q&MG) not serving on the study management team to support Quality Assurance activities and/or regulatory agency inspections

- Biostatisticians and programmers employed by contract research organizations (CROs) who develop datasets and outputs for development of randomization schedule, DMC, IND safety reporting purposes

Should Gilead staff receive unblinded information, they will maintain the confidentiality of the unblinded information and will not communicate the information to blinded sites or participants as specified in Gilead standard operating procedures (SOPs) documents

5.1.3. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain the treatment assignment for that participant directly from IRT (refer to Investigator Site File or IRT unblinding instructions). In the event the IRT system is down, the investigator can reference the IRT Site User Manual for technical support details. Gilead recommends but does not require that the investigator contact the Gilead medical monitor or designee before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant's emergency medical care. The rationale for unblinding must be clearly explained in source documentation along with the date on which the treatment assignment was obtained. The investigator is requested to inform the medical monitor or designee promptly in case of any treatment unblinding not discussed in advance.

Blinding of study treatment is critical to the integrity of this clinical study. Therefore, if a participant's treatment assignment is disclosed to the investigator, the participant will have study treatment discontinued. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

5.2. Description and Handling of Semaglutide

5.2.1. Formulation

The drug product formulation for the SEMA solution for injection has the composition shown in Table 2. All ingredients other than the active drug substance are commonly used excipients. Semaglutide solution for injection is a colorless or almost colorless liquid, free from turbidity and essentially free from particulate matter.

Table 2. Composition of Semaglutide Solution for Injection

Name of ingredient	Function	Pharmacopeia
Drug substance		
Semaglutide	Active ingredient	Novo Nordisk A/S
Other ingredients		
Disodium hydrogen phosphate, dihydrate	Buffering agent	USP/Ph. Eur
Propylene glycol	Isotonic agent	USP/JP/Ph. Eur
Phenol	Preservative	USP/JP/Ph. Eur
HCl	pH adjustment	USP/JP/Ph. Eur
NaOH	pH adjustment	USP/JP/Ph. Eur
Water for injection	Solvent	USP/JP/Ph. Eur

JP = Japanese Pharmacopeia; Ph. EUR = European Pharmacopeia; USP = United States Pharmacopeia

Placebo-to-match SEMA has an identical formulation to the study drug product except that it does not contain any active ingredient.

5.2.2. PDS290 Pen Injector for Semaglutide for Use in Clinical Studies

5.2.2.1. Device Information

The PDS290 pen injector for SEMA/PTM SEMA is a dial-a-dose prefilled device integrated with a 3.0 mL cartridge filled with SEMA 3.0 mg/mL/PTM SEMA. The pen injector can deliver doses from 1 to 80 dose steps in increments of 1. The user can dial up and down in order to adjust a dose. The accuracy of dosing is ensured according to the international standard for needle-based injection systems, EN ISO 11608-1.

The PDS290 pen injector for SEMA/PTM SEMA can be used multiple times until either the in-use time (up to 8 weeks when stored at 8 to 30 °C) has passed or the cartridge is empty, whichever comes first. The pen injector works in conjunction with all variants of NovoTwist® and NovoFine® disposable needles. A new needle must be attached before and discarded after each injection.

Specific instructions for correct handling of the PDS290 pen injector for SEMA/PTM SEMA are included in the directions for use provided to study sites and to be provided directly to participants. Storage instructions are printed on the drug product label and are also provided in the Investigator Site File. Investigators must ensure that these instructions are strictly followed.

5.2.2.2. Regulatory Status

The PDS290 pen injector for SEMA/PTM SEMA complies with relevant standards and regulations. Several other variants of PDS290 pen injectors have been approved worldwide since 2010 for SC injection of insulins (under the brand name modifier FlexTouch®), growth hormone (under the brand name modifier FlexPro®) and GLP-1 products (Saxenda®, Ozempic®).

5.2.2.3. Existing Clinical Data

The adequate safety and performance of the PDS290 pen injector for SEMA (3.0 mg/mL) for the intended purpose are demonstrated through the literature review as well as the analysis of human factors engineering data and postmarketing safety data for the PDS290 pen injector family.

In the Phase 2 Study GS-US-454-5533, 108 participants were randomized to 1 of 5 treatment groups, all of which included SEMA administered with the PDS290 pen injector (3.0 mg/mL). Overall, no participants experienced any treatment-emergent pen injector related AEs over the 24-week treatment period.

It is concluded that the PDS290 pen injector for SEMA (3.0 mg/mL) provides a favorable benefit-risk profile for administration of SEMA/PTM SEMA in NASH clinical studies.

5.2.3. Storage and Handling

Semaglutide must be stored at 2 to 8 °C. Exposure to light and freezing must be avoided. Under these storage conditions, SEMA will retain full biological activity until the expiry date stated on the label. The SEMA solution should be inspected visually for particulate matter and discoloration prior to administration. The pen injector should be discarded if either is present. Only use the SEMA solution for injection if it has colorless or almost colorless appearance free from turbidity and essentially free from particulate matter.

5.2.4. Shelf-life and In-use Time for Semaglutide in PDS290

The shelf -life of SEMA in the PDS290 pen injector is up to 36 months when stored between 2 to 8 °C. The study drug should not be used after the expiry date unless an extension of the expiry date has been notified and received in writing from Gilead. The in-use time is up to 8 weeks when stored at 8 to 30 °C. Do not refrigerate after first use of the pen injector. Exposure to excessive heat and light as well as freezing must be avoided during use.

5.3. Description and Handling of CILO/FIR

5.3.1. Formulation

CILO/FIR 30 mg/20-mg tablets are a FDC product containing 30 mg of CILO (free-form equivalent) and 20 mg of FIR. The tablets contain CILO tromethamine salt (GS-967402), FIR, and inactive ingredients mannitol, microcrystalline cellulose, crospovidone, magnesium stearate and film-coating materials polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, and red iron oxide. The CILO/FIR 30 mg/20-mg tablets are orange, capsule-shaped, debossed with "GSI" on 1 side and "7674" on the other side.

Placebo-to-match CILO/FIR 30 mg/20-mg tablets are identical in size, shape, color and appearance to the active CILO/FIR 30 mg/20-mg tablets and contain inactive ingredients lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and film-coating materials polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, and red iron oxide.

5.3.2. Packaging and Labeling

CILO/FIR 30 mg/20 mg and PTM CILO/FIR 30 mg/20-mg tablets are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drug(s) to be distributed to sites in the US and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products) for CTD, or Annex 6 for CTR, as applicable, and/or other local regulations.

5.3.3. Storage and Handling

CILO/FIR 30 mg/20-mg tablets and PTM CILO/FIR 30 mg/20-mg tablets should be stored below 30 °C (86 °F). Storage conditions are specified on the label. Until dispensed to the participants, all bottles of study drug should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.4. Labeling of Study Drug

Study drug to be distributed to sites in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.5. Dosage and Administration of CILO/FIR and SEMA

The administration of study drug will be recorded in the source documentation and in the electronic case report form (eCRF).

Study drug dosing and administration will occur as follows:

- Group A: SEMA 3.0 mg/mL administered SC with prefilled pen injector once weekly and 1 CILO/FIR 30 mg/20-mg tablet administered orally once daily, both without regard to food
- Group B: SEMA 3.0 mg/mL administered SC with prefilled pen injector once weekly and 1 PTM CILO/FIR 30 mg/20-mg tablet, administered orally once daily, both without regard to food

- Group C: PTM SEMA 3.0 mg/mL administered SC with prefilled pen injector once weekly and 1 CILO/FIR 30 mg/20-mg tablet administered orally once daily, both without regard to food

- Group D: PTM SEMA 3.0 mg/mL administered SC with prefilled pen injector once weekly and 1 PTM CILO/FIR 30 mg/20-mg tablet administered orally once daily, both without regard to food

5.5.1. Dosage and Administration of CILO/FIR

CILO/FIR 30 mg/20 mg and PTM CILO/FIR 30 mg/20-mg tablets will be provided by Gilead. Participants will take a CILO/FIR 30 mg/20-mg tablet (if applicable) at approximately the same time each day, with or without food, swallowed whole with water. Participants taking a concomitant acid reducing agent, including histamine 2 receptor antagonists, should be instructed to take the CILO/FIR 30 mg/20-mg tablet with food. For CILO/FIR 30 mg/20 mg, a dose will be considered missed if the participant cannot take the complete dose within 12 hours of their regular dosing time. If a participant misses a dose, the participant should take their next dose at the regular dosing time.

5.5.2. Dosage and Administration of Semaglutide

Semaglutide 3.0 mg/mL in PDS290 pen injectors will be manufactured and provided by Novo Nordisk, Inc. Participants should be instructed to inject SEMA SC once weekly on the same day of the week throughout the study. Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. Participants should be encouraged to inject in the same area throughout the study but changing between the left and right side is allowed.

If a single dose of study drug is missed, it should be administered as soon as possible, provided the time to the next scheduled dose is at least 48 hours. If a single dose is missed and the next scheduled dose is less than 48 hours away, the participant should not administer a dose until the next scheduled dose. A single missed dose should not affect the previously scheduled dosing day of the week.

If 2 or 3 consecutive doses are missed, the participant should be encouraged to restart study drug if considered safe per the investigator's discretion and if the participant does not meet any of the discontinuation criteria. The study drug should be resumed as early as possible. The starting dose for resuming study drug is at the investigator's discretion; however, if more than 3 consecutive doses are missed, consideration should be given to resuming study drug at a reduced dose. In case of questions related to resuming study drug, the investigator should consult the medical monitor or designee.

5.5.3. Management of Semaglutide Dose Escalation

After randomization, SEMA will be initiated with a starting value of 8 (0.24 mg) as shown on the dose counter of the prefilled pen injector for the first 4 weeks (4 doses), and subsequently the value will be increased every 4 weeks. All participants must aim to reach the recommended target dose of SEMA 2.4 mg once weekly.

Table 3. Semaglutide Dose-Escalation Schedule

Product	Dose	Volume	Value Shown in the Dose Counter	Duration (by Study Visit)
Semaglutide 3.0 mg/mL PDS290	0.24 mg	80 µL	8	Day 1* up to Week 4
Semaglutide 3.0 mg/mL PDS290	0.50 mg	170 µL	17	Week 5 up to Week 8
Semaglutide 3.0 mg/mL PDS290	1.0 mg	340 µL	34	Week 9 up to Week 12
Semaglutide 3.0 mg/mL PDS290	1.7 mg	570 µL	57	Week 13 up to Week 16
Semaglutide 3.0 mg/mL PDS290	2.4 mg	800 µL	80	Week 17 up to Week 72

* Participant will take first dose of study drug on-site at Day 1.

If a participant does not tolerate the planned 4-week dose-escalation regimen due to GI AEs or for other reasons as judged by the investigator, the participant may stay longer at any dose level. It is recommended that the investigator aim for a maximum of 1 extra week on any dose level below the target dose level. If the dose escalation is delayed, the investigator should evaluate weekly if the dose can be escalated to the next planned level until the target dose of 2.4 mg once weekly is reached.

If a participant does not tolerate the recommended target dose of 2.4 mg once weekly, the participant may stay at the lower dose level. This is only permitted if the participant would otherwise discontinue study drug completely and if it is considered safe for the participant to continue on study drug, per the investigator's discretion. It is recommended that the participant makes at least 1 additional attempt to escalate to the recommended target dose of 2.4 mg once weekly, per the investigator's discretion.

It is recommended that the investigator contact the medical monitor or designee in case of persistent deviations from the planned escalation.

5.6. Prior and Concomitant Medications

All concomitant medication will be recorded in the source documents and eCRFs. This includes medications taken within 30 days prior to screening and any taken during the study to the end of the follow-up period.

The following medications are prohibited:

- Any investigational medication within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to screening and through the end of study is prohibited. Participation in an investigational study of a device may be approved by the medical monitor or designee

- Any compound that is approved or under investigation for the treatment of NASH, or another liver disease associated with liver fibrosis such as PBC or PSC (eg, obeticholic acid, resmetirom, pegbelfermin, aldafermin), excluding antidiabetic medications, within 30 days or within 5 half-lives of the compound (whichever is longer) prior to screening and throughout the study

- Any medication or supplement prescribed for weight loss within 30 days prior to screening and throughout the study

Participants on a vitamin E regimen ≥ 800 IU/day or on pioglitazone must be on a stable dose, in the opinion of the investigator, for at least 180 days prior to the historical or screening liver biopsy. Participants taking antidiabetic medications must be on a stable dose, in the opinion of the investigator, for at least 90 days prior to the historical or screening liver biopsy. If possible, the doses of these medications should remain stable through the end of treatment.

Treatment with GLP-1 RAs, including SEMA, is prohibited in the period 90 days prior to the date of the qualifying historical or screening liver biopsy. Treatment with nonstudy-related GLP-1 RAs is prohibited from 90 days prior to the date of screening through the end of study.

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters organic anion transporting polypeptide 1B1 or 1B3, potent or moderate inducers of CYP2C8, or potent inducers of CYP3A4) with drug(s) may result in PK interactions resulting in increases or decreases in exposure of study drug(s).

Examples of medications that are prohibited or which require special administration considerations are listed below in Table 4.

Table 4. Examples of Prohibited Medications and Agents Requiring Special Administration Considerations From 30 Days Prior to Day 1 Through End of Treatment[a]

Drug Class	Prohibited	Agents Requiring Special Administration Considerations
Immunosuppressants	Chronic systemic corticosteroids[b], tacrolimus, sirolimus, cyclosporine, mycophenolate, methotrexate	—
Acid reducing agents	—	Antacids[c], histamine 2 receptor antagonists[d], proton pump inhibitors[d]
Antibiotics	Clarithromycin, erythromycin	Azithromycin[e]
Anticonvulsants[f]	Phenobarbital, phenytoin, carbamazepine, oxcarbazepine	—
Antimycobacterials[f]	Rifampin, rifabutin, rifapentine[g], isoniazid	—
Bile acid sequestrants[h]	—	Cholestyramine, colestipol[g], colesevelem[g], colestilan
Endothelin receptor agonists	Bosentan	—
Herbal/natural supplements[f]	—	St John's Wort, echinacea, Chinese herb sho-saiko-to (or xiao-shai-hu-tang)
Other[f]	Glycyrrhetinic acid[i] (active ingredient of British licorice)	Gemfibrozil[g], modafinil

a Not all of these example medications may be approved where the study is being conducted; please refer to local product information.
b Intra-articular, topical, nasal, or inhaled routes are allowed. Chronic systemic use of corticosteroids equivalent to prednisone > 10 mg/day for > 2 weeks is not allowed. Use for ≤ 2 weeks total is allowed.
c Antacids that directly neutralize stomach pH (ie, Tums, Maalox) are permitted but may not be taken within 4 hours (before or after) oral study drug administration.
d Participants taking an acid reducing agent (including histamine 2 receptor antagonists) should take oral study drug with food.
e Chronic azithromycin therapy is prohibited.
f May result in an increase or decrease in the concentration of study drug.
g Not approved in Japan.
h Bile acid sequestrants are permitted but may not be taken within 4 hours (before or after) oral study drug administration.
i Glycyrrhizae Radix is a traditional herbal medicine commonly prescribed in Japan as an anti-inflammatory agent and contains glycyrrhetinic acid, which confers a mineralocorticoid excess state (sodium retention and potassium wasting).
Please refer to current World Health Organization guidelines for a complete list of medications from prohibited classes listed above.

5.6.1. Participants Treated With Insulin at Screening

Throughout the study, insulin dose should be titrated at the discretion of the investigator. For the individual participant, increasing the insulin dose before 2 weeks after the end of the final dose escalation should be avoided, unless required to control acute hyperglycemia and acute diabetic complications.

5.6.2. Participants With Screening $HbA_{1c} \leq 8.0\%$ Treated With Insulin

Participants with screening $HbA_{1c} \leq 8.0\%$ treated with SEMA in combination with insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia can be lowered by reducing the dose of insulin, and a dose reduction at randomization and throughout the study should be considered at the discretion of the investigator.

5.6.3. Participants Treated With Sulfonylureas at Screening

Participants treated with SEMA in combination with a sulfonylurea may have an increased risk of hypoglycemia. The risk of hypoglycemia can be lowered by reducing the dose of sulfonylurea, and a dose reduction at randomization and throughout the study should be considered at the discretion of the investigator.

5.7. Accountability for Investigational Medicinal Product and Devices

The investigator is responsible for ensuring adequate accountability of all used and unused study drug and devices, including empty containers. This includes acknowledgment of receipt of each shipment of study drug and devices (quantity and condition). All used and unused study drug and devices (including empty containers) dispensed to participants must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug/devices
- The date, participant number, and the study drug/device kit number dispensed
- The date, quantity of used and unused study drug/devices returned, along with the initials of the person recording the information

5.7.1. Investigational Medicinal Product and Device Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant enrolled in the study (from screening through the follow-up visit) are presented in tabular form in Appendix 11.5 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the CRO.

6.1. Participant Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Participants will be screened within 8 weeks before randomization to determine eligibility for the study. The screening period may be extended with the explicit approval of the medical monitor or designee.

Screening laboratory tests may be repeated once within the screening period, at the discretion of the investigator, prior to administration of study drug. Lipid management may be initiated, and repeat testing of triglycerides is permitted at the discretion of the investigator as noted in Section 7.7.4.

Participants should be instructed to fast (no food or drink, except water), from midnight (00:00) or earlier, as appropriate, on the evening prior to obtaining blood samples to ensure an approximate 8-hour fast prior to the sample collection.

The following will be performed and documented at screening:

- Obtain written informed consent before initiation of any screening procedures
- Review inclusion and exclusion criteria
- Obtain screening number from IRT
- Obtain medical history including, but not limited to, information related to the following: type 2 diabetes, NAFLD, NASH, and any history of hepatic decompensation

- Perform fundoscopic examination for participants with type 2 diabetes diagnosed prior to the date of the screening visit OR based on screening visit results ($HbA_{1c} \geq 6.5\%$ or fasting plasma glucose ≥ 126 mg/dL, confirmed on repeat testing). If there has been worsening of the participant's visual function since an historical fundoscopic examination in the opinion of the investigator, then the fundoscopic examination must be repeated prior to Day 1 for eligibility. If a qualifying historical fundoscopic examination is available, this assessment is not required to be repeated at screening

- Perform liver biopsy or provide liver tissue from historical liver biopsy (per inclusion criterion 3) for central pathologists' evaluation

- Complete physical examination (PE)

- Assessment of ascites and HE

- Record vital signs, body weight, and height

- Measure hip and waist circumference

- Conduct electrocardiogram (ECG)

- Calculation of the CP and MELD scores

- Abdominal ultrasound for evaluation of presence of HCC, gallstones, or other hepatobiliary disease, if applicable (Section 6.8.13). A historical ultrasound within 90 days of the screening visit is acceptable

- Measure liver stiffness using FibroScan

- Provide lifestyle counseling

- Obtain blood samples for

  — Chemistry panel, including creatine kinase (CK)

  — Hematology panel

  — Coagulation panel

  — Lipid panel

  — Glycemic panel

— Fasting plasma glucose (fasting plasma glucose ≥ 126 mg/dL should be confirmed on repeat testing if type 2 diabetes is previously undiagnosed as determined by medical history)*

— HbA_{1c} (HbA_{1c} ≥ 6.5% should be confirmed on repeat testing if type 2 diabetes is previously undiagnosed as determined by medical history)*

* Note that if a participant with previously undiagnosed type 2 diabetes has confirmed fasting glucose or HbA_{1c} above the protocol-specified criteria for diabetes, treatment should be initiated in accordance with guidelines from the American Diabetes Association {American Diabetes Association 2020a, American Diabetes Association 2020b} or other society, per investigator discretion.

— eGFR by MDRD

— ELF test

— HIV-1, HBV, and HCV serology

— Biomarkers

— Serum pregnancy test (only for women of childbearing potential)

— Serum follicle-stimulating hormone (FSH) test (only for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)

- Collect urine samples for:

  — Drug screen for amphetamines, cocaine, and opiates (eg, heroin, morphine)

  — Biomarkers

- Provide stool sample collection kit

- Record all concomitant medications that the participant has taken within 30 days prior to screening

- SARS-CoV-2 RT-PCR test in participants who have not completed a series of an authorized COVID-19 vaccination regimen prior to screening

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-mandated procedures on the Adverse Events eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. See Section 7, Adverse Events and Toxicity Management, for additional details.

Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 8 weeks after screening for randomization into the study.

6.2.2. Day 1 Visit

Participants returning to the clinic for randomization on Day 1 should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the Day 1 visit to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.

After review of inclusion and exclusion criteria to confirm continued eligibility, participants will be randomized to study drug assignment and receive their participant identification number via the IRT prior to their first dose of study drug.

Prior to dosing at the Day 1 visit, the following will be performed and documented:

- Collect PROs (Functional Assessment of Chronic Illness Therapy [FACIT] Fatigue Questionnaire, NASH-CHECK, Patient Global Impression of Severity [PGIS] for Fatigue and Pain, and 36-Item Short Form Survey [SF-36]). It is recommended that PROs be completed prior to any other study procedures being performed
- Symptom-driven PE
- Assessment of ascites and HE
- Record vital signs and body weight
- Measure hip and waist circumference
- Calculation and review of the CP and MELD scores
- Provide lifestyle counseling
- Obtain blood samples for:
  - Chemistry panel
    - (qualifying eGFR by MDRD)
  - Hematology panel
  - Coagulation panel
  - Lipid panel
  - Glycemic panel
  - HbA_{1c}

  - ELF test
  - Biomarkers
- Collect urine samples for:
  - Pregnancy test (only for women participants of childbearing potential)
  - Biomarkers
- Collect stool sample for biomarkers
- CCI [redacted]
- Record all concomitant medications the participant has taken since the previous visit
- Record any SAEs and all AEs related to protocol-mandated procedures occurring since the screening visit
- Dispense study drug to the participant and provide instruction on appropriate dosing and administration; participant will take the Day 1 dose of study drug on site
- Counseling regarding importance of continued adherence to study procedures (Section 6.8.15)

6.3. Randomization

Randomization will be stratified by the presence or absence of type 2 diabetes as determined by medical history or based on screening laboratory values if previously undiagnosed (ie, $HbA_{1c} \geq 6.5\%$ or fasting plasma glucose ≥ 126 mg/dL, confirmed on repeat testing), and by ELF score (≥ 11.30 or < 11.30 during screening).

6.4. Treatment Assessments

Week 4 through Week 72 assessments will be performed as described at the time points indicated in the Study Procedures Table (Appendix 11.5).

6.5. Unscheduled Visits

Unscheduled assessments may be performed at the discretion of the investigator.

Participants who will have any laboratory assessments performed should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the visit to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.

Additional assessments may be performed at the discretion of the investigator or as recommended by the medical monitor or designee. At a minimum, the following will be performed and documented:

- Symptom-driven PE
- Assessment of ascites and HE
- Record vital signs and body weight
- Obtain blood samples for:
  - Chemistry panel
    - (eGFR by MDRD)
  - Hematology panel
  - Coagulation panel
- Record all concomitant mediations that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

In cases where the unscheduled visit is performed for the primary purpose of safety evaluation (eg, SAE follow-up), collection of a single PK sample (anytime predose or postdose) is recommended. The timing of the PK sample in relation to the last dose of study drug should be documented.

If the unscheduled visit is performed for the sole purpose of the distribution of study drug, the assessments noted above do not need to be performed.

6.5.1. Premature Discontinuation of Study Drug

If a participant discontinues study drug dosing (eg, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study. Study drug discontinuation criteria are listed in Section 3.5.

Participants who prematurely discontinue study drug may return for an unscheduled visit at the discretion of the investigator or request of the medical monitor or designee for a safety evaluation. Participants should be encouraged to complete their remaining study visits in accordance with the Study Procedures Table (Appendix 11.5), if appropriate.

6.5.2. Early Termination Visit

Participants who prematurely discontinue from the study should complete an ET visit within 30 days of the last dose of study drug and a follow-up visit 5 weeks after the ET visit. Participants who previously discontinued study drug and continued to complete study visits should return for an ET visit even if it has been more than 30 days since their last dose of study drug.

Participants should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the visit to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.

The following must be performed and documented:

- Symptom-driven PE (see Section 11.9.1 for France-specific text.)
- Assessment of ascites and HE
- Record vital signs and body weight
- Measure hip and waist circumference
- Calculation of the CP and MELD scores
- Provide lifestyle counseling
- Obtain blood samples for:
  - Chemistry panel
    - (eGFR by MDRD)
  - Hematology panel
  - Coagulation panel
  - Lipid panel
  - Glycemic panel
  - HbA_{1c}
  - PK (single sample anytime predose or postdose; the timing of the PK sample in relation to the last dose of study drug should be documented)
- Collect urine pregnancy test (only for women participants of childbearing potential per 11.6)

- CCI [redacted]
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Review of study drug dosing compliance

The following should be performed unless completed within 12 weeks of ET visit:

- Perform abdominal ultrasound for presence of HCC, gallstones, or other hepatobiliary disease
- Measure liver stiffness by FibroScan

The following can be performed and documented at the discretion of the investigator:

- Collect PROs (FACIT-Fatigue, NASH-CHECK, PGIS and Patient Global Impression of Change [PGIC] for Fatigue, PGIS and PGIC for Pain, SF-36). It is recommended that PROs be completed prior to any other study procedures being performed
- Perform liver biopsy
- Conduct ECG
- Perform fundus examination
- Obtain blood samples for:
  - ELF test
  - Biomarkers
- Collect urine sample for:
  - Biomarkers

See Section 11.9.1 for France-specific text

6.6. Follow-up Visit

Participants will return for a follow-up visit 5 weeks after the Week 72 or ET visit.

Participants should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the visit to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.

The following will be performed and documented at the follow-up visit:

- Symptom-driven PE
- Assessment of ascites and HE
- Record vital signs and body weight
- Measure hip and waist circumference
- Calculation of the CP and MELD scores
- Provide lifestyle counseling
- Obtain blood samples for:
  - Chemistry panel
    - (eGFR by MDRD)
  - Hematology panel
  - Coagulation panel
  - Lipid panel
  - Glycemic panel
  - HbA_{1c}
  - Biomarkers
- Collect urine samples for:
  - Pregnancy test (only for women participants of childbearing potential per Appendix 11.6)
  - Biomarkers
- Record all concomitant medications that the participant has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit

6.7. Study Visit Windows

Windows for study visits are presented in Table 5.

Table 5. Study Visit Windows

Study Visit	Window
Screening visit	≤ 8 weeks prior to Day 1, window begins with the signing of the informed consent.
Day 1	Day of randomization and the first dose of study drug. All study visits are calculated based on the Day 1 date.
Week 48 fundoscopic examination	± 14 days
Week 72 (including fundoscopic examination)	−14 days
All study visits from Week 4 to Week 60	± 3 days
ET visit	Within 30 days of last dose of study drug. Participants who previously discontinued study drug, continued to complete study visits and are discontinuing from the study should return for an ET visit even if it has been more than 30 days since their last dose of study drug.
Follow-up visit	5 weeks after Week 72 or ET visit (± 7 days).

ET = early termination

6.8. Description of Study Assessments

6.8.1. Clinical Laboratory Assessments

Fasting is required prior to all study visits.

6.8.1.1. Chemistry Panel

Albumin, ALT, AST, ALP, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine (reflex to serum enzymatic creatinine, as applicable), lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, and GGT.

6.8.1.2. Hematology Panel

Hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential (absolute and percentage) including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume.

6.8.1.3. Coagulation Panel

Prothrombin time, partial thromboplastin time, and INR.

6.8.1.4. Glycemic Panel

Insulin, homeostasis model assessment of insulin resistance (HOMA-IR) based on fasting glucose and insulin, and C-peptide.

6.8.1.5. Lipid Panel

Triglycerides, total cholesterol, HDL, non-HDL, LDL, and VLDL by Friedewald calculation.

6.8.1.6. Additional Tests

HbA_{1c} (reflex to serum fructosamine, as applicable), HIV-1 (reflex to HIV-1 RNA, if applicable), HBV (HBsAg) and HCV (reflex to HCV RNA, as applicable) serology, eGFR as calculated by MDRD, urine drug screen (for amphetamines, cocaine, opiates), serum pregnancy test, FSH, reflex direct LDL (if triglycerides are > 400 mg/dL), CK, and CCI [redacted].

6.8.1.7. Biomarkers

Including but not limited to CRP, NMR LipoProfile®, ELF score, CK18 M30, CK18 M65, Pro-C3, CTXIII, total serum bile acids, apolipoproteins, SomaSignal NASH tests, and, potentially, levels of hepatic genes and proteins. Bile acids and the representation of microbial populations may also be tested in stool samples.

6.8.1.8. Urine Samples

Microalbumin, creatinine, microalbumin/creatinine ratio; at screening for amphetamines, cocaine, methadone, and opiates; urine pregnancy test (reflex to serum beta human chorionic gonadotropin), and stored for CCI [redacted].

6.8.1.9. Pharmacokinetic Assessments

6.8.1.9.1. Single PK Sampling

Single PK plasma samples will be collected and archived for PK analysis of CILO and FIR (and their metabolites, as applicable). Samples will be collected at Week 4 (15 minutes to 3 hours postdose), Week 24 (anytime postdose), Week 48 (predose), Week 60 (15 minutes to 3 hours postdose), Week 72 (predose), the ET visit (anytime), and at unscheduled visits (anytime) that are performed for the purpose of safety evaluation (eg, SAE follow-up). For PK sampling at Weeks 4, 48, 60, and 72, participants should be reminded not to take their oral study drug until advised to do so at their clinic visit.

6.8.1.10. Blood Sample Collection

In the course of the assessments outlined above which require collection of blood samples, a total of at least 12 blood sample collections will be required throughout the study. Approximate total blood volume collected at each visit and overall is outlined below.

- Screening, Day 1, and Week 24: 81.8 mL
- Week 4 and Week 60: 14.8 mL
- Week 8, Week 16, and Week 36: 8.8 mL
- Week 12: 75.8 mL
- Week 48 and Week 72: 87.8 mL
- ET: 89.3 mL
- Follow-up: 73.3 mL

Approximate total blood volume of 552.8 mL may be drawn for study purposes from screening through Week 72, and approximate total blood volume of 626.1 mL may be drawn from screening through follow-up.

6.8.2. Physical Examination

A complete PE should include source documentation of general appearance, and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; neurological.

The focus of a symptom-driven PE will be determined by the investigator based on participant complaint. For example, if a participant complains of a cough, a respiratory examination should be performed. If consistent with pneumonia (eg, rales or crackles are identified), then an AE would be documented.

Assessments to evaluate for the presence of ascites and HE should be performed at every visit.

Measurements for height, body weight, and hip and waist circumference will be collected at specified time points.

See Section 11.9.1 for France-specific text.

6.8.3. Fundoscopic Examination

For participants with type 2 diabetes diagnosed prior to the date of the screening visit OR based on a screening visit $HbA_{1c} \geq 6.5\%$, participants must have no evidence of uncontrolled and potentially unstable retinopathy or maculopathy as determined by a fundoscopic examination performed within 90 days prior to screening visit through Day 1. If there has been worsening of the participant's visual function since a historical fundoscopic examination in the opinion of the investigator, then the fundoscopic examination must be repeated prior to Day 1 for eligibility. Pharmacological pupil dilation is a requirement unless using a digital fundus photography camera specified for nondilated examination.

Fundoscopic examinations should be performed and interpreted by a qualified ophthalmologist or optometrist. The report must be reviewed by the investigator or medically qualified delegate, with documentation of the below criteria on the fundoscopic examination result report or in the participant's medical record:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

If a fundoscopic examination matching this description has been performed within 90 days prior to the date of the screening visit, or between screening visit and Day 1, the procedure does not need to be repeated unless there has been worsening of visual function since the last examination in the opinion of the investigator. The results must be available prior to Day 1.

If the dilated fundoscopic examination is performed before the participant has signed the informed consent form (ICF), it must be documented in the medical records that the reason for performing the procedure was not related to this study.

For participants with type 2 diabetes only, the fundoscopic examination will be repeated at Weeks 48 and 72, or ET visit, per investigator’s discretion.

6.8.4. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature.

Blood pressure will be measured using the following standardized process:

- Participant should sit for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery
- Measure and record the blood pressure to the nearest 2 mm Hg mark on the manometer or to the nearest whole number on an automatic device

6.8.5. Clinical Liver Assessments

MELD and CP scores will be derived from the central laboratory values obtained at each visit.

Sites will use the central laboratory values to calculate CP at each visit, including screening, to assess eligibility and at subsequent visits to identify CP > 6 requiring confirmation and treatment discontinuation (Section 3.5). Assessment of ascites and HE will be determined by the site at all visits, as described in Table 6, and will be entered into the eCRFs. Dialysis in the preceding week will also be determined by the site at each visit. Hepatic encephalopathy will be assessed using the West Haven Criteria (Appendix 11.4).

The MELD score calculation will be performed by the central laboratory. If the central laboratory is unable to perform the MELD score calculation, sites may use the central laboratory values to calculate the MELD score. MELD should be monitored by the site at each visit to identify potential criteria for liver transplantation, as described in study drug discontinuation criteria (Section 3.5).

MELD will be calculated using the following formula:

MELD score = 10 × ([0.378 × ln (total bilirubin mg/dL)] + [1.12 × ln (INR)] + [0.957 × ln (serum creatinine mg/dL)] + 0.643)

- Serum creatinine in µmol/L will be converted to mg/dL by multiplying by 0.01131. The resulting value will be rounded to 2 decimal places
  - If the serum creatinine is < 1.00 mg/dL, use 1.00 as the serum creatinine value
  - If the serum creatinine is > 4.00 mg/dL or if the participant has had 2 or more dialysis treatments within the preceding week, use 4.00 as the serum creatinine value
  - If the “Creatinine (Rate Blanked)” is resulted as “Icteric–Test Not Performed” by the central laboratory, use the serum enzymatic creatinine value
- Total bilirubin in µmol/L will be converted to mg/dL by multiplying by 0.05848 and the resulting total bilirubin value to 1 decimal place
  - If the total bilirubin is < 1.0 mg/dL, use 1.0 as the total bilirubin value
- If the INR is < 1.0, use 1.0 as the INR value

The online calculator https://www.mdcalc.com/meld-score-original-pre-2016-model-end-stage-liver-disease may also be used

Table 6. Child-Pugh Classification of the Severity of Cirrhosis

Score	1	2	3
HE	**None** No encephalopathy and not on any treatment for HE	**Medication-Controlled** Participant is lethargic, may have moderate confusion Participant is receiving medical therapy for HE	**Medication-Refractory** Marked confusion/incoherent, rousable but sleeping or comatose
Ascites	**None** No ascites and not on treatment for ascites	**Mild/Moderate** Abdominal distension Medication for ascites	**Severe (Diuretic-Refractory)** Visible clinically
Bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
INR	< 1.7	1.7 to 2.3	> 2.3

HE = hepatic encephalopathy; INR = international normalized ratio

A CP score is obtained by adding the score for each parameter.

CP Class: A = 5 to 6 points
B = 7 to 9 points
C = 10 to 15 points

Participants who have a CP score > 6 at any time during the study confirmed as soon as possible, preferably within 72 hours, (unless due to an alternative etiology such as Gilbert's syndrome or therapeutic anticoagulation) must discontinue study drug (Section 3.5).

6.8.6. Estimated Glomerular Filtration Rate Using MDRD Equation

Estimated glomerular filtration rate will be calculated by the central laboratory. If the central laboratory is unable to perform the eGFR calculation, eGFR may also be calculated by the sites.

Estimated glomerular filtration rate is calculated by the MDRD equation (conventional units) {Levey 2006}

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.212\ \text{if Black})$$

S_{cr} = serum creatinine (mg/dL)

6.8.7. Genomic Testing

From participants who agree to participate and provide consent, blood samples will be collected at the Day 1 visit, Week 48, Week 72, and ET (if applicable) for genomic testing, including DNA methylation.

6.8.8. Pregnancy Testing

All women of childbearing potential (as defined in Appendix 11.6) will have a serum pregnancy test at screening. Urine pregnancy testing will occur at Day 1 (prior to dosing) and every 4 weeks thereafter. Starting at the Week 4 visit, every 4 weeks (± 3 days) urine pregnancy testing may be performed at home in between clinic visits, where possible, or in clinic, if at home pregnancy tests are unavailable. In the event of a positive urine pregnancy result, participants will be instructed to stop study drug immediately (if applicable), inform their study physician, and return to the clinic as soon as possible for a serum pregnancy test.

6.8.9. PRO Measures

It is recommended that these questionnaires, as possible, be completed prior to any other study assessments at each visit. The participant should read the questionnaires and record the answers independently.

6.8.9.1. FACIT-Fatigue (Version 4)

The FACIT-Fatigue PRO measure is a 13-item questionnaire designed to measure fatigue and lifestyle-related consequences of fatigue, with all responses reported on a scale of 0 to 4. Participants are directed to respond to each question based on their experience in the previous 7 days.

6.8.9.2. NASH-CHECK (Version 1.0)

The NASH-CHECK is a 28-item PRO measure designed to measure symptoms and health-related quality of life including day-to-day activities, emotions, and lifestyle in participants with NASH. Symptoms of NASH are reported on a scale of 0 to 10, with participants asked to report the severity of the symptom at its worst over the previous 7 days. Participants are directed to respond to additional questions related to day-to-day activities, emotions and lifestyle based on quality of life in the prior 7 days.

6.8.9.3. Patient Global Impression of Severity (PGIS) Fatigue

For the PGIS Fatigue, participants will be asked to rate their overall impression of their fatigue during the past week on a 4-point scale from “none” to “severe”. The PGIS Fatigue will be used as an anchor to support the interpretation of the FACIT-Fatigue questionnaire and NASH-CHECK fatigue items.

6.8.9.4. Patient Global Impression of Change (PGIC) Fatigue

For the PGIC Fatigue, participants will be asked to rate their overall impression of how their fatigue has changed since they started taking the study medication, on a 7-point scale from “very much improved” to “very much worsened”. The PGIC Fatigue will be used as an anchor to support the interpretation of the FACIT-Fatigue and NASH-CHECK fatigue items.

6.8.9.5. PGIS Pain

For the PGIS Pain, participants will be asked to rate their overall impression of their upper abdominal (stomach) pain during the past week on a 4-point scale from “none” to “severe”. The PGIS Pain will be used as an anchor to support the interpretation of the NASH-CHECK upper abdominal (stomach) pain item.

6.8.9.6. PGIC Pain

For the PGIC Pain, participants will be asked to rate their overall impression of how their upper abdominal (stomach) pain has changed since they started taking the study medication, on a 7-point scale from “very much improved” to “very much worsened”. The PGIC Pain will be used as an anchor to support the interpretation of the NASH-CHECK upper abdominal (stomach) pain item.

6.8.9.7. SF-36 (Version 1.0)

The SF-36 consists of 36 questions to measure functional health and well-being from the participant’s point of view, and comprises 8 health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health). These health domain scales contribute to the physical health and mental health summary measures.

6.8.10. Liver Stiffness Measured by Transient Elastography (FibroScan)

The acceptable elastographic method is vibration-controlled transient elastography (FibroScan). FibroScan examinations will be performed at the screening visit and Weeks 24, 48, and 72. The median liver stiffness in kPa, interquartile range/median value (IQR/M), and success rate (number of valid shots/total number of shots) will be recorded. Where available, the median CAP and the IQR of CAP values will be recorded. For ET visits, a FibroScan assessment should be performed unless performed within 12 weeks of the ET visit.

For individual participants, the same probe should be used for all assessments. Probe size should be determined based on the machine probe size recommendation at the screening assessment. The same probe size should then be used at all subsequent assessments. If the machine being used does not recommend a probe size, an extra-large probe should be used at all examinations if available. If an extra-large probe is not available and/or a valid result cannot be obtained, an examination with the medium probe should be performed and the result recorded. At least 3 hours fasting is recommended prior to all FibroScan assessments.

All FibroScan assessments should be performed with SmartExam turned off. If this is not possible, then data files must be saved and sent to Echosens for reprocessing into the standard format.

6.8.11. Liver Biopsy

All possible attempts should be made to acquire a liver biopsy specimen of at least 2.0 cm in length to ensure accurate staging of fibrosis and other histological parameters. If a screening or Week 72 liver biopsy is deemed unevaluable by the central pathologists, it may be repeated.

If a historical biopsy is used to determine eligibility, it must have been done within 180 days of the screening visit. All liver biopsies will be sent to a central laboratory and will be evaluated by central pathologists. For inclusion, historical or screening liver biopsy samples must be deemed evaluable and consistent with cirrhosis (F4) and NASH (defined as the presence of steatosis Grade ≥ 1, hepatocellular ballooning Grade ≥ 1, and lobular inflammation Grade ≥ 1, according to NAS) in the opinion of the central pathologists.

Week 72 liver biopsy results will be blinded to the investigator and participant.

If a liver biopsy is performed per standard of care outside of protocol-mandated assessments, all possible attempts should be made to submit the biopsy specimen to the central pathologists for evaluation.

Please refer to the Investigator Site File for additional information.

6.8.12. Lifestyle Counseling

Lifestyle modifications such as weight loss via diet and increased exercise can be effective in the treatment of NASH. All participants will receive counseling, provided by the investigator or a qualified health professional, regarding lifestyle modifications including the maintenance of a healthy diet and participation in regular exercise. Appendix 11.7 provides lifestyle recommendations developed by the American College of Cardiology/American Heart Association {Arnett 2019}. Weight loss surgeries or procedures may not be performed during the study.

6.8.13. Abdominal Ultrasound

Abdominal ultrasound for evaluation of presence of HCC, gallstones, or other hepatobiliary disease will be performed at the screening visit. A historical ultrasound within 90 days of the screening visit is acceptable. On-study abdominal ultrasounds should be performed at Weeks 24, 48, and 72. For ET visits, an abdominal ultrasound should be performed unless performed within 12 weeks of the ET visit.

6.8.14. Electrocardiogram

Standard 12-lead ECG assessments will be performed. The investigator will review the ECGs for any clinically significant abnormalities to ensure participant safety. Abnormal ECG findings that are considered clinically significant by the investigator and meet the definition of an AE should be reported and recorded in the AE eCRF page.

6.8.15. Counseling Regarding Adherence to Study Procedures

Participants should be encouraged at each visit to remain in the study and adhere to study procedures. Participants who prematurely discontinue study drug are encouraged to return for an unscheduled visit at the discretion of the investigator or request of the medical monitor or designee for a safety evaluation. Participants who prematurely discontinue study drug should be encouraged to complete their remaining study visits in accordance with the Study Procedures Table (Appendix 11.5), if appropriate. Site-specific plans will be developed to include relevant participant retention strategies.

6.9. Sample Storage

Stored biological samples may be used by Gilead or its research partner(s) for future testing to provide additional data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period of up to 15 years. If participants provide additional specific consent for optional future research, residual PK, and biomarker samples may be used for exploratory future research. Residual samples will be destroyed no later than 15 years after end of study or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered any study drug, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.5).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.5)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs

7.1.2. Serious Adverse Events

An SAE is defined as an event that results in the following:

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- In-patient hospitalization or prolongation of existing hospitalization (not including hospitalization for elective surgery)

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening- or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse
- A hypoglycemic episode is considered an SAE if it meets any criteria above of it requires the assistance of another person to correct (eg, to administer carbohydrate)

7.1.3. Serious Adverse Drug Reaction

A serious adverse drug reaction (SADR) is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

7.1.4. Adverse Events of Special Interest

7.1.4.1. Hypoglycemic Episodes

Hypoglycemic episodes must be reported as an AE on the AE eCRF according to Section 7.3.2. Additionally, participants with type 2 diabetes must be instructed to measure their blood glucose in connection with symptoms of hypoglycemia. Plasma glucose values ≤ 70 mg/dL (≤ 3.9 mmol/L) should be reported as a hypoglycemic episode. This information and other relevant clinical data must be reported on a hypoglycemic episode eCRF. If the hypoglycemic episode meets seriousness criteria, the event must be reported on the eCRF and to Gilead PS as an SAE (Section 7.4.1.1).

7.1.4.2. Other Adverse Events of Special Interest

Additional adverse events of special interest (AESI), including both serious and nonserious AEs, will require submission of additional information on an event specific eCRF. These events include acute pancreatitis, acute gallbladder disease, malignant neoplasm (not including localized basal or squamous cell cancer or other localized non-melanoma skin cancer or carcinoma in situ of the cervix), diabetic retinopathy, and any case where a participant meets criterion for study drug withholding as specified in Section 7.7.3.

7.1.4.3. Liver-Related Clinical Events

Additional information for participants experiencing clinically significant liver events should be reported on an event specific eCRF. These events include clinically significant ascites,

complications of ascites such as spontaneous bacterial peritonitis, hepato-pleural effusion or others, variceal hemorrhage, hepatic encephalopathy, worsening of MELD score to ≥ 15 (confirmed on repeat testing), liver transplantation, or liver-related death. Participants who discontinue study drug due to evidence of hepatic decompensation must be followed until they stabilize clinically.

7.1.5. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE (which includes situations of missed dose), a medication error with an AE, an intercepted medication error, or a potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively which is above the maximum recommended dose per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes**: there is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** the AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE Toxicity Grading Scale. For each episode, the highest grade attained (1, 2, 3, 4, or 5) should be reported as defined in the Toxicity Grading Scale (provided in the Investigator Site File).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until at least 5 weeks after last administration of study drug and report them on the eCRFs as instructed.

All AEs should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and to Gilead PS (Section 7.4.1). This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 5 weeks of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug or device, the investigator should promptly document and report the event to Gilead PS.

7.3.4. Study Drug Special Situations Reports

All study drug special situations reports (SSRs) that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead PS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours:

Gilead PS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information within 24 hours of the investigator's knowledge to Gilead PS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record the SSR information electronically, record the SSR on the paper special situation reporting form and transmit within 24 hours to:

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead PS utilizing the paper special situations report form to:

Gilead PS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies in female study participants and/or female partners of male participants who are identified after initiation of study drug and throughout the study (including the posttreatment follow-up period) and through 5 weeks after last study drug dosage to Gilead PS using the pregnancy outcome report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead PS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead PS using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PS at the contact listed above.

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy of the participant (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to the Gilead PS; however, if the SAE occurs in a partner, the pregnancy-related SAE will not be captured in eCRF but should be reported via the paper pregnancy outcome report form.

Refer to Appendix 11.6 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs (which may be in the form of line listings), SADRs, or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter or a quarterly SAE line listing notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Toxicity Grading Scale. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

Information regarding handling of specific laboratory abnormalities in this study is provided in Section 7.7.

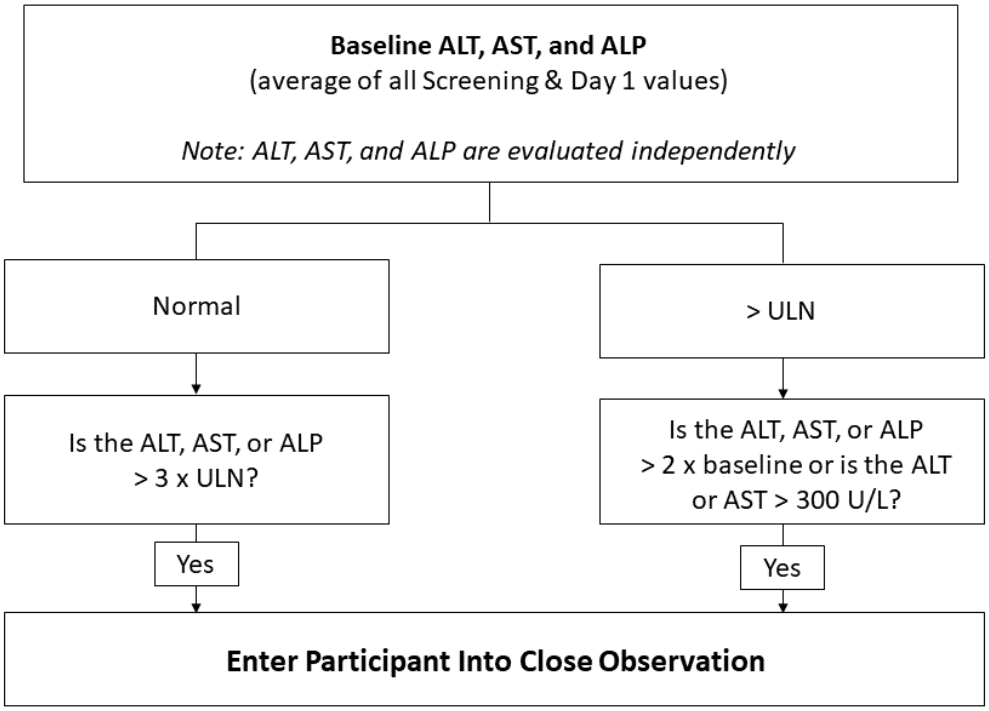
7.7. Toxicity Management

7.7.1. Monitoring for DILI

Baseline values for liver tests (ALT, AST, ALP, and total bilirubin) will be determined by the central laboratory by averaging the values obtained during screening and at Day 1. At baseline, some participants may have liver biochemistry levels above the ULN. Please refer to the Laboratory Manual or individual participant laboratory reports for gender- and age-specific reference ranges.

Unless the clinical context points towards an apparent etiology other than DILI or progressive liver disease, on-treatment elevations of ALT, AST, and/or ALP should be confirmed on repeat testing within 72 hours of initial results (or as soon as possible). Participants with repeat ALT, AST, or ALP elevations must be placed into close observation as shown in Figure 4 below.

Figure 4. On-Treatment Monitoring Requiring Close Observation



ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

7.7.2. Close Observation

Close observation includes the following:

- Obtaining a more detailed history of symptoms and prior or concurrent disease, including the presence of any hepatic decompensation events including hepatic encephalopathy, clinically relevant ascites, variceal bleeding, and spontaneous bacterial peritonitis
- Obtaining a history of concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations, and recreational drugs), alcohol use, and special diets
- Obtaining a history of exposure to environmental chemical agents
- Ruling out other causes of liver disease as needed (eg, obtain viral hepatitis panel, imaging for evaluation of biliary tract disease) and if relevant in the opinion of the investigator
- Monitoring liver biochemistries at least twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the participant is asymptomatic

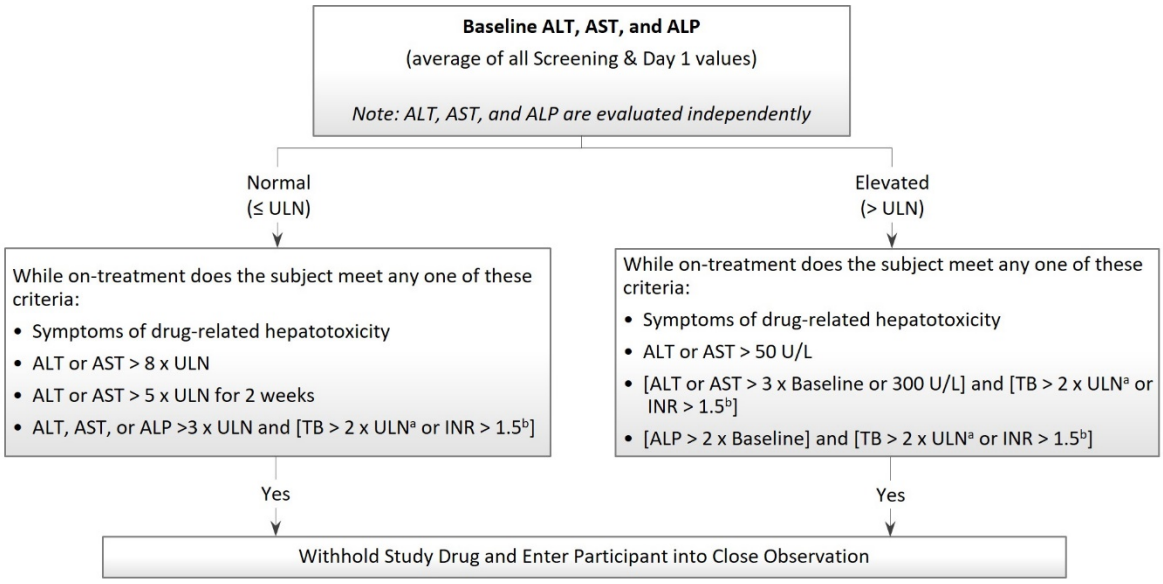
During a period of close observation for DILI, study drug may be continued at the discretion of the investigator and the medical monitor, or designee

7.7.3. Study Drug Withholding

If on-treatment elevations of ALT, AST, ALP, total bilirubin, and/or INR meet the criteria specified in Figure 5, and are confirmed on repeat testing within 72 hours of results (or as soon as possible), and no cause other than progressive liver disease and/or DILI is immediately apparent, the participant must be placed into close observation as described in Section 7.7.2 and study drug must be withheld.

Additionally, any participant who develops signs or symptoms of liver toxicity (eg, right upper quadrant pain, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%) which are suspected by the investigator to be drug related, must be placed into close observation and study drug must be withheld, or permanently discontinued if the participant meets discontinuation criteria outlined in Section 3.5. In cases where close observation as outlined in Section 7.7.3 is not possible, study drug must be discontinued. Participants who discontinue study drug due to suspected hepatotoxicity must be followed until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels, until there is a satisfactory explanation for the changes observed, or for 90 days after drug discontinuation, whichever is longer.

Figure 5. On-Treatment Monitoring Requiring Study Drug Withholding



ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TB = total bilirubin; ULN = upper limit of normal

a Unless participant has Gilbert's syndrome or other cause of unconjugated hyperbilirubinemia, in which case a direct bilirubin > 2 × baseline value (average of screening and Day 1 values) will be used instead of total bilirubin.

b If not on therapeutic anticoagulation (eg, warfarin). If on therapeutic anticoagulation, INR criteria is disregarded.

In all cases where a participant meets criteria for study drug withholding as outlined in Figure 5, additional information must be submitted on an event of special interest eCRF, as described in Section 7.1.4.2. Additionally, if study drug is withheld due to meeting criteria in Figure 5 the case will be reported to the DMC and study drug may not be reintroduced prior to review by the DMC and subsequent approval of the medical monitor, or designee. In cases where study drug is

resumed and clinical or laboratory criteria outlined in Figure 5 are again met, study drug must be permanently discontinued.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the medical monitor or designee. Whether or not considered treatment related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or are considered irreversible, or until there is a satisfactory explanation for the changes observed.

All clinically significant Grade 3 or 4 laboratory abnormalities, including laboratory parameters not included in Figure 4 or Figure 5, should be confirmed on repeat testing as soon as possible, and preferably within 72 hours of the initial results. For AEs associated with laboratory abnormalities, the event should be graded based on the clinical severity in the context of the underlying conditions, which may or may not agree with the grading of the laboratory abnormality.

Any questions regarding toxicity management should be directed to the medical monitor or designee.

7.7.4. Lipid Management

7.7.4.1. Triglycerides

If a participant has fasting serum triglycerides > 250 mg/dL during screening, management of hypertriglyceridemia may be initiated and/or modified at investigator discretion in accordance with standard of care as described below. Repeat testing may be performed during the screening window after triglyceride management. Prior to Day 1, fasting serum triglycerides must be confirmed to be ≤ 250 mg/dL for the participant to be eligible for the study.

Standard of care management of hypertriglyceridemia includes, but is not limited to, lifestyle counseling and treatment with a fibrate (eg, FENO), and/or VAS, and/or a statin. In the Phase 2 Study GS-US-384-3914, FENO 145 mg once daily was well tolerated and mitigated increases in serum triglycerides in participants with NASH treated with CILO+FIR (Section 1.5.2.1.1).

On-treatment elevations of fasting serum triglycerides > 500 mg/dL should be confirmed on repeat testing as soon as possible, preferably within 48 hours, and all study drugs should be withheld upon confirmation of levels > 500 mg/dL. In these cases, to manage observed triglyceride elevations, participants may initiate or dose escalate (if possible) fibrate therapy. Participants may resume study drug if fasting serum triglycerides are subsequently confirmed to be < 250 mg/dL after at least 2 weeks of fibrate therapy, if deemed safe in the opinion of the investigator. If after resumption of study drugs, serum triglycerides are again confirmed > 500 mg/dL and the participant is already on a maximal dose of fibrate, the participant must discontinue study drugs permanently (Section 3.5).

Treatment with statins may be associated with muscle injury (ie, myopathy); this risk is increased in participants concurrently treated with a fibrate. If a participant is receiving treatment with both a fibrate and a statin, serum CK should be measured at study visits and appropriate clinical evaluation, including interruption of statin therapy, should be initiated if muscle injury is suspected {Brewster 2007, Kashani 2006, Rosenson 2017}. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of serum CK. Participants should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after interruption of statin therapy.

Any questions regarding triglyceride management, including management of suspected myopathy, should be directed to the medical monitor or designee.

7.7.4.2. Low-Density Lipoprotein Cholesterol

If at any time while on treatment, a participant has a persistent increase above baseline in fasting serum LDL cholesterol, initiation or dose modification of a statin (or other lipid lowering medication), should be considered. Questions regarding LDL changes and considerations of lipid modifying therapy should be directed to the medical monitor or designee. Appendix 11.8 presents recommendations from academic societies on assessing cardiovascular risk that may be used to guide management.

7.7.5. Pruritus Management

The development or worsening of pruritus during the study is a consideration for participants with liver disease. Management of pruritus may include nonpharmacologic interventions (eg, skin moisturization, minimized heat exposure, avoidance of skin irritants, scratch reduction), oral antihistamines, and/or bile acid sequestrants. Bile acid sequestrants must be taken more than 4 hours before or after oral study drug dosing, as described in Table 4. Administration of oral study drug with a light-fat meal may also be beneficial.

7.7.6. Child-Pugh Score

If a participant has an increase in their CP score to > 6, this should be confirmed with repeat testing as soon as possible, preferably within 72 hours. If confirmed, and an etiology for these findings other than progressive liver disease cannot be identified (eg, therapeutic anticoagulation), the participant must discontinue study drug (Section 3.5).

7.7.7. MELD Score

If a participant has an increase in their MELD score to > 12, this should be confirmed with repeat testing, preferably within 72 hours. If confirmed, and an etiology for these findings other than progressive liver disease cannot be identified (eg, therapeutic anticoagulation), the participant must discontinue study drug (Section 3.5).

8. STATISTICAL CONSIDERATIONS

This section provides a high-level description of the planned analyses, assessed statistical power with assumptions, and any applicable multiplicity adjustments. Additional details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

Objectives are listed in Section 2. Endpoints are listed in Section 3.1

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate whether the combination of SEMA with the FDC of CILO/FIR causes fibrosis improvement in participants with compensated cirrhosis due to NASH as compared with placebo

The secondary objectives of this study are as follows:

- To confirm the contribution of CILO/FIR to fibrosis improvement in participants treated with the combination of SEMA and CILO/FIR by comparing with participants treated with SEMA alone
- To evaluate whether the combination of SEMA with the FDC of CILO/FIR causes NASH resolution (defined as lobular inflammation of 0 or 1 and hepatocellular ballooning of 0) in participants with compensated cirrhosis due to NASH, as compared with placebo
- To confirm the contribution of SEMA to NASH resolution in participants treated with the combination of SEMA and CILO/FIR by comparing with participants treated with CILO/FIR alone

CCI

[redacted]

8.1.2. Endpoints

8.1.2.1. Primary Endpoint

The primary endpoint is:

- ≥ 1-stage improvement in fibrosis (according to the NASH CRN classification) without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation) at Week 72 in the SEMA+CILO/FIR versus placebo groups

8.1.2.2. Secondary Endpoints

The secondary endpoints of this study are as follows:

- ≥ 1-stage improvement in fibrosis (according to the NASH CRN classification) without worsening of NASH at Week 72 in SEMA+CILO/FIR versus participants treated with SEMA alone

- NASH resolution (defined as lobular inflammation of 0 or 1 and hepatocellular ballooning of 0) at Week 72 in the SEMA+CILO/FIR versus placebo groups

- NASH resolution at Week 72 in SEMA+CILO/FIR versus participants treated with CILO/FIR alone

CCI [redacted]

8.2. Planned Analyses

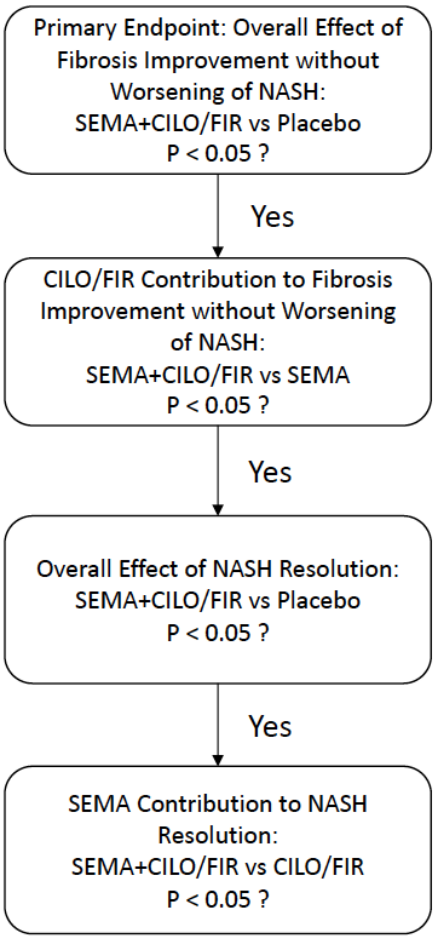
8.2.1. Final Analysis

The final analysis will be performed at Week 72, after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint defined in Section 8.1.2.1 will be conducted at the time of the final analysis and will be tested at the 2-sided 0.05 significance level (Figure 6).

8.2.2. Multiplicity Adjustments

The multiple testing strategy for the primary endpoint and the secondary endpoints is described below and presented graphically in Figure 6.

Figure 6. Multiple Testing Strategy



CILO = cilofexor (GS-9674); firsocostat = FIR (GS-0976); NASH = nonalcoholic steatohepatitis; SEMA = semaglutide

The family-wise type I error rate (FWER) will be controlled through the following sequential testing procedure at a 2-sided significance level of 0.05 (equivalent to 1-sided 0.025).

First, the primary endpoint will be tested at a 2-sided significance level of 0.05. The primary objective will be considered achieved if the superiority of SEMA+CILO/FIR versus placebo for the primary endpoint as described below is met.

1) The overall effect of the primary histologic efficacy endpoint of fibrosis improvement without worsening of NASH will be compared between the SEMA+CILO/FIR and placebo groups at Week 72 at a 2-sided significance level of 0.05. Superiority of SEMA+CILO/FIR versus placebo will be demonstrated through the test of the null hypothesis of equal responder proportions against the alternative hypothesis of a higher proportion in the SEMA+CILO/FIR group.

If the primary objective is achieved, the secondary efficacy endpoints will be tested sequentially in the following order at a 2-sided significance level of 0.05. If superiority is achieved for a secondary endpoint, the next secondary endpoint will be evaluated; otherwise, testing of the remaining secondary endpoint(s) will cease.

1) The contribution of CILO/FIR to fibrosis improvement ≥ 1-stage without worsening of NASH will be evaluated by comparing the SEMA+CILO/FIR and SEMA groups for this endpoint at a 2-sided significance level of 0.05. Superiority of SEMA+CILO/FIR versus SEMA will be demonstrated through the test of the null hypothesis of equal responder proportions against the alternative hypothesis of a higher proportion in the SEMA+CILO/FIR group.

2) The overall effect of NASH resolution will be compared between the SEMA+CILO/FIR and placebo groups at Week 72 at a 2-sided significance level of 0.05. Superiority of SEMA+CILO/FIR versus placebo will be demonstrated through the test of the null hypothesis of equal responder proportions against the alternative hypothesis of a higher proportion in the SEMA+CILO/FIR group.

3) The contribution of SEMA to NASH resolution will be evaluated by comparing the SEMA+CILO/FIR and CILO/FIR groups for this endpoint at a 2-sided significance level of 0.05. Superiority of SEMA+CILO/FIR versus CILO/FIR will be demonstrated through the test of the null hypothesis of equal responder proportions against the alternative hypothesis of a higher proportion in the SEMA+CILO/FIR group.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analyses will be the Full Analysis set (FAS) which includes all participants who were randomized into the study and received at least 1 dose of study drug.

Participants who receive study drug other than that to which they were randomized will be analyzed according to the treatment group to which they were randomized.

8.3.1.2. Safety

The primary analysis set for safety analyses will include all participants who received at least 1 dose of study drug. Participants who received study drug other than that to which they were randomized will be analyzed according to the study drug received. All data collected during treatment plus 35 days after last dose of study drug will be included in the safety summaries.

8.3.1.3. Pharmacokinetics

The PK Analysis Set includes concentration data from the single samples drawn at each visit.

The PK Analysis Set will include all randomized participants who took at least 1 dose of study drug and for whom concentration data of analytes CILO, FIR, and their respective metabolites, as applicable, are available. The PK Analysis Set will be used for analyses of population PK.

8.3.1.4. Biomarkers

The Biomarker Analysis Set will include data from participants in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3.2. Data Handling Conventions

Participants with missing data on the primary, secondary, and CCI [redacted] at Week 72 will be imputed using reference-based multiple imputation method. The handling of intercurrent events for the primary, secondary, and CCI [redacted]

Where appropriate, safety data for participants who did not complete the study will be included in summary statistics. For example, if a participant received study drug, the participant will be included in a summary of AEs according to the treatment received; otherwise, if the participant is not dosed then they will be excluded from the summary. If safety laboratory results for a participant are missing for any reason at a time point, the participant will be excluded from the calculation of summary statistics for that time point. If the participant has no available value before the first dosing time, then the participant will be excluded from the calculation of summary statistics for the predose value and the change from predose values.

Values for missing safety laboratory data will not be imputed; however, a missing baseline result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the baseline value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities.

Values for missing vital signs data (except for body weight and blood pressure) will not be imputed; however, a missing baseline result will be replaced with a screening result, if available.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, age, body weight, height, and BMI.

Baseline data will include a summary of randomization stratification groups (presence or absence of diabetes; ELF score ≥ 11.30 or < 11.30), and other disease characteristic variables.

Any discrepancies between the IRT randomization stratification groups and the group assigned based on data entered in the database will be listed.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The following hybrid estimand of composite and treatment policy strategies (Table 7) will be used as the primary estimand for the primary histologic endpoint. Treatment policy strategy will be used to handle all intercurrent events except all-cause mortality and any liver-related clinical events that occur prior to the Week 72 liver biopsy, which will be handled by a composite strategy.

Table 7. Estimand Strategy for Primary Histologic Endpoint

Primary Endpoint	Hybrid Composite/Treatment Policy Strategy
Population	All participants in the FAS as defined in Section 8.3.1.1 who had nonmissing baseline fibrosis (only for the primary outcome below) and NAS components used in the definition of the endpoints.
Patient-level outcomes to be measured	A binary response of ≥ 1-stage fibrosis improvement without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation) at Week 72 in the SEMA+CILO/FIR vs placebo groups based on the reading of baseline and postbaseline biopsies by the central pathologists.
Measure of intervention effect and handling of intercurrent events	Composite policy estimand: participants who experienced a liver-related clinical event[a] or died due to any cause (all-cause mortality) prior to the Week 72 liver biopsy are assumed to be nonresponders for the primary endpoint. Treatment policy estimand: the value of outcome measure is used regardless of the occurrence of intercurrent events other than death or a liver-related clinical event[a] prior to the Week 72 liver biopsy (ie, dose interruption/reduction, protocol deviation, or premature study drug discontinuation).
Population level summary measure	Difference in proportions of ≥ 1-stage fibrosis improvement without worsening of NASH responders between SEMA+CILO/FIR and placebo groups.
Main estimators	A stratified Mantel-Haenszel test will be used to compare the difference in proportions of participants who meet the primary endpoint at Week 72 between SEMA+CILO/FIR and placebo, adjusting for baseline diabetes status and ELF score (≥ 11.30 or < 11.30). Participants who experienced a liver-related clinical event or died due to any cause (all-cause mortality) prior to the Week 72 liver biopsy are considered nonresponders. Participants who had missing data at Week 72 due to reasons other than death or a liver-related clinical event[a] will be handled by reference-based imputation, ie, a method of multiple imputation that is informed by data from placebo participants. It is thereby assumed that participants in either treatment group without an observed outcome have the same chances of meeting the endpoint as participants in the placebo group with an observed outcome.

CILO = cilofexor (GS-9674); ELF = enhanced liver fibrosis; FAS = Full Analysis Set; FIR = firsocostat (GS-0976); MELD = Model for End-Stage Liver Disease; NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; SEMA = semaglutide

a Liver-related clinical events include evidence of progression to decompensated cirrhosis, liver transplantation, or qualification for liver transplantation on basis of MELD score (Section 7.1.4.3).

8.5.2. Secondary Analyses

The same estimand strategy as described for the primary endpoint will be used for the secondary endpoints. To demonstrate the contribution of CILO/FIR to fibrosis improvement without worsening of NASH, Table 8 describes the estimand strategy for the secondary endpoint of ≥ 1-stage fibrosis improvement without worsening of NASH at Week 72 in the SEMA+CILO/FIR versus SEMA groups.

Table 8. Estimand Strategy for Secondary Endpoint 1: Fibrosis Improvement Without Worsening of NASH at Week 72 in the SEMA+CILO/FIR Versus SEMA Groups

Secondary Endpoint 1	Hybrid Composite/Treatment Policy Strategy
Population	All participants in the FAS as defined in Section 8.3.1.1 who had nonmissing baseline fibrosis and NAS components used in the definition of the endpoints.
Patient-level outcomes to be measured	A binary response of ≥ 1-stage fibrosis improvement without worsening of NASH at Week 72 in the SEMA+CILO/FIR vs SEMA groups, based on the reading of baseline and postbaseline biopsies by the central pathologists.
Measure of intervention effect and handling of intercurrent events	Composite policy estimand: participants who experienced a liver-related clinical event[a] or died due to any cause (all-cause mortality) prior to the Week 72 liver biopsy are assumed to be nonresponders for the secondary endpoint. Treatment policy estimand: The value of outcome measure is used regardless of the occurrence of intercurrent events other than death or a liver-related clinical event[a] prior to the Week 72 liver biopsy (ie, dose interruption/reduction, protocol deviation, or premature study drug discontinuation).
Population level summary measure	Difference in proportions of ≥ 1-stage fibrosis improvement without worsening of NASH responders between the SEMA+CILO/FIR and SEMA groups.
Main estimators	A stratified Mantel-Haenszel test will be used to compare the difference in proportions of participants who meet fibrosis improvement without worsening of NASH at Week 72 between the SEMA+CILO/FIR and SEMA groups, adjusting baseline diabetes status and ELF score (≥ 11.30 or < 11.30). Participants who experienced a liver-related clinical event or died due to any cause (all-cause mortality) prior to the Week 72 liver biopsy are considered nonresponders. Participants who had missing data at Week 72 due to reasons other than death or a liver-related clinical event[a] will be handled by reference-based imputation.

CILO = cilofexor (GS-9674); ELF = enhanced liver fibrosis; FAS = Full Analysis Set; FIR = firsocostat (GS-0976); MELD = Model for End-Stage Liver Disease; NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; SEMA = semaglutide

a Liver-related clinical events include evidence of progression to decompensated cirrhosis, liver transplantation, or qualification for liver transplantation on basis of MELD score (Section 7.1.4.3).

To evaluate the overall effect of NASH resolution, Table 9 describes the estimand strategy for the secondary endpoint of NASH resolution at Week 72 in the SEMA+CILO/FIR versus placebo groups.

Table 9. Estimand Strategy for Secondary Endpoint 2: NASH Resolution at Week 72 in the SEMA+CILO/FIR Versus Placebo Groups

Secondary Endpoint 2	Hybrid Composite/Treatment Policy Strategy
Population	All participants in the FAS as defined in Section 8.3.1.1 who had nonmissing baseline NAS components used in the definition of the endpoints.
Patient-level outcomes to be measured	A binary response of NASH resolution (defined as lobular inflammation of 0 or 1 and hepatocellular ballooning of 0) at Week 72 in the SEMA+CILO/FIR vs placebo groups, based on the reading of baseline and postbaseline biopsies by the central pathologists.
Measure of intervention effect and handling of intercurrent events	Composite policy estimand: experienced a liver-related clinical event[a] or died due to any cause (all-cause mortality) prior to the Week 72 liver biopsy are assumed to be nonresponders for the secondary endpoint. Treatment policy estimand: the value of outcome measure is used regardless of the occurrence of intercurrent events other than death or a liver-related clinical event[a] prior to the Week 72 liver biopsy (ie, dose interruption/reduction, protocol deviation, or premature study drug discontinuation).
Population level summary measure	Difference in proportions of NASH resolution responders between SEMA+CILO/FIR and placebo groups.
Main estimators	A stratified Mantel-Haenszel test will be used to compare the difference in proportions of participants who meet NASH resolution at Week 72 between SEMA+CILO/FIR and placebo, adjusting for baseline diabetes status and ELF score (≥ 11.30 or < 11.30). Participants who experienced a liver-related clinical event or died due to any cause (all-cause mortality) prior to the Week 72 liver biopsy are considered nonresponders. Participants who had missing data at Week 72 due to reasons other than death or a liver-related clinical event[a] will be handled by reference-based imputation.

CILO = cilofexor (GS-9674); ELF = enhanced liver fibrosis; FAS = Full Analysis Set; FIR = firsocostat (GS-0976); MELD = Model for End-Stage Liver Disease; NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; SEMA = semaglutide

a Liver-related clinical events include evidence of progression to decompensated cirrhosis, liver transplantation, or qualification for liver transplantation on basis of MELD score (Section 7.1.4.3).

To demonstrate the contribution of SEMA to NASH resolution, Table 10 describes the estimand strategy for the secondary endpoints of NASH resolution at Week 72 in the SEMA+CILO/FIR versus CILO/FIR groups.

Table 10. Estimand Strategy for Secondary Endpoint 3: NASH Resolution at Week 72 in the SEMA+CILO/FIR Versus CILO/FIR Groups

Secondary Endpoint 3	Hybrid Composite/Treatment Policy Strategy
Population	All participants in the FAS as defined in Section 8.3.1.1 who had nonmissing baseline NAS components used in the definition of the endpoints.
Patient-level outcomes to be measured	A binary response of NASH resolution at Week 72 in the SEMA+CILO/FIR vs CILO/FIR groups, based on the reading of baseline and postbaseline biopsies by the central pathologists.
Measure of intervention effect and handling of intercurrent events	Composite policy estimand: experienced a liver-related clinical event[a] or died due to any cause (all-cause mortality) prior to the Week 72 liver biopsy are assumed to be nonresponders for the secondary endpoint. Treatment policy estimand: the value of outcome measure is used regardless of the occurrence of intercurrent events other than death or a liver-related clinical event[a] prior to the Week 72 liver biopsy (ie, dose interruption/reduction, protocol deviation, or premature study drug discontinuation).
Population level summary measure	Difference in proportions of NASH resolution responders between SEMA+CILO/FIR and CILO/FIR groups.
Main estimators	A stratified Mantel-Haenszel test will be used to compare the difference in proportions of participants who meet NASH resolution at Week 72 between SEMA+CILO/FIR and CILO/FIR, adjusting for baseline diabetes status and ELF score (≥ 11.30 or < 11.30). Participants who experienced a liver-related clinical event or died due to any cause (all-cause mortality) prior to the Week 72 liver biopsy are considered nonresponders. Participants who had missing data at Week 72 due to reasons other than death or a liver-related clinical event[a] will be handled by reference-based imputation.

CILO = cilofexor (GS-9674); ELF = enhanced liver fibrosis; FAS = Full Analysis Set; FIR = firsocostat (GS-0976); MELD = Model for End-Stage Liver Disease; NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis; SEMA = semaglutide

a Liver-related clinical events include evidence of progression to decompensated cirrhosis, liver transplantation, or qualification for liver transplantation on basis of MELD score (Section 7.1.4.3).

8.5.3. Sensitivity Analysis

Sensitivity analyses on the primary and secondary histologic endpoints will be described in the statistical analysis plan.

CCI [redacted]

8.6. Safety Analysis

Safety will be assessed during the study through the reporting of AEs, clinical laboratory tests, and vital sign assessments at various time points during the study. Concomitant medication usage will also be assessed throughout the study.

All safety data collected on or after the date that study drug was first administered up to the date of last dose of study drug plus 35 days will be summarized by treatment group (according to the study drug received). Data for the pretreatment will be included in data listings if applicable. In addition to cumulative incidence proportions, exposure-adjusted incidence rates will be provided for GI and pruritus-related AEs, as well as selected AEs of special interest (as described in Section 7.1.3).

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA. System organ class (SOC), high-level group term, high-level term, PT, and lower-level term will be attached to the clinical database. Adverse event severity will be graded using the CTCAE.

Events will be summarized on the basis of the date of onset for the event. Treatment-emergent adverse events (TEAEs) will be defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 35 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug

Summaries (number and percentage of participants) of TEAEs by SOC and PT will be provided by treatment group. Treatment-emergent adverse events will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug and study will be summarized and listed.

All AEs collected during the course of the study will be presented in data listings with a field for treatment-emergent event (yes/no).

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) by treatment group and study visit along with the corresponding change from baseline values

Graded laboratory abnormalities will be defined using the grading scheme in the CTCAE.

The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time after baseline up to and including the date of last dose of study drug plus 35 days, will be summarized by treatment group. If baseline data are missing, any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the participant has been discontinued from treatment for at least 35 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital sign measurements and 12-lead ECG will be summarized by treatment group and listed by participant.

8.7. Pharmacokinetic Analysis

Plasma concentrations of CILO, FIR, and their respective metabolites, as applicable, will be listed, if available. Data from this study may be combined with data from other studies in a population PK meta-analysis.

8.8. Biomarker Analysis

Descriptive statistics of biomarker results and change from baseline will be provided at each sampling time by dose group. Point estimates and 95% CIs may be calculated.

CCI [redacted]

CCI [redacted]

8.9. Sample Size

The power calculation is based on the estimated proportions of participants in the SEMA+CILO/FIR group to achieve the primary endpoint at Week 72 as compared with the placebo group. Assuming the proportion of participants in the SEMA+CILO/FIR and placebo groups to achieve fibrosis improvement ≥ 1-stage without worsening of NASH at Week 72 is 35% and 12%, respectively, with a sample size of 120 participants in the SEMA+CILO/FIR group and 80 participants in the placebo group, the study has 97% power to detect a difference at a 2-sided significance level of 0.05.

If the primary endpoint is achieved, the contribution of CILO/FIR to fibrosis improvement ≥ 1-stage without worsening of NASH will be evaluated by comparing the SEMA+CILO/FIR and SEMA groups for this endpoint. Assuming the proportion of participants to achieve ≥ 1-stage fibrosis improvement without worsening of NASH at Week 72 is 35% and 20% in the SEMA+CILO/FIR and SEMA groups, respectively, with a sample size of 120 participants in each group, the study has 74% power to detect a difference at a 2-sided significance level of 0.05.

If the contribution of CILO/FIR to fibrosis improvement ≥ 1-stage without worsening of NASH is demonstrated, the overall effect of NASH resolution will be evaluated by comparing the SEMA+CILO/FIR versus placebo groups. Assuming the proportion of participants in the SEMA+CILO/FIR and placebo groups to achieve NASH resolution at Week 72 is 45% and 10%, respectively, the study has > 99% power to detect a difference at a 2-sided significance level of 0.05.

If the superiority of SEMA+CILO/FIR versus placebo for the overall effect of NASH resolution is achieved, the contribution of SEMA to NASH resolution will be evaluated by comparing the SEMA+CILO/FIR and CILO/FIR groups for this endpoint. Assuming the proportion of participants to achieve NASH resolution at Week 72 is 45% and 15% in the SEMA+CILO/FIR and CILO/FIR groups, respectively, with a sample size of 120 participants in each group, the study has 99% power to detect a difference at a 2-sided significance level of 0.05.

The power calculations described above are based on Pearson's chi-square test using a normal approximation.

8.10. Data Monitoring Committee

An external DMC that consists of 2 hepatologists and a statistician will review the progress of the study, perform interim, and as necessary, ad hoc reviews of safety data, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or whether the study should continue with modifications.

The DMC will convene after at least 55 participants have completed their Week 4 visit and approximately every 6 months thereafter to monitor the study for safety events.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

In the course of ongoing safety monitoring, if at any point any of the below criteria are met, an urgent meeting of the DMC will be held to determine whether the study should proceed as planned, proceed with modification, or be terminated:

- ≥ 2 participants develop CTCAE Grade 4 pancreatitis (life threatening) deemed related to study drug(s) by the investigator
- ≥ 2 participants develop the same CTCAE Grade 4 unexpected AE (by PT) deemed related to study drug(s) by the investigator
- Any participant develops a CTCAE Grade 5 unexpected AE (death) deemed related to study drug(s) by the investigator

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. INVESTIGATOR RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with sponsor or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify sponsor of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The ICF will inform participants about genomic testing and/or planned sample retention. [redacted]

9.1.5. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB, IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. Note: the investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, CRFs/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs/eCRFs, IB, IEC, and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification
- Documentation that participant meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator

in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the EDC system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory).
The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB or IEC in accordance with local requirements and receive documented IRB or IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.6).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical study agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries in the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the medical monitor or designee immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Termination

Both Gilead and the investigator (for their clinical site) reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority(ies), and IRB or IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

11.1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

CLINICAL STUDY PROTOCOL ACKNOWLEDGMENT

GS-US-454-6075: A Phase 2, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study Evaluating the Safety and Efficacy of Semaglutide, and the Fixed-Dose Combination of Cilofexor and Firsocostat, Alone and in Combination, in Subjects With Compensated Cirrhosis (F4) due to Nonalcoholic Steatohepatitis (NASH)

Amendment 2, 26 October 2023

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD Sr Director, Clinical Development	*[See appended electronic signature]* Signature
[See appended electronic signature] Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

11.2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

    a) Participants may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any participant visits. Without study drugs, the participant would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: study drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue on study drug as determined by the principal investigator (PI). A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study participants if permitted by local ethics committee (EC)/institutional review boards (IRB)/regulatory authority as applicable and with sponsor's approval.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug participant would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: the sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

2) Participant safety monitoring and follow-up:

    a) Participants may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

        Mitigation plan: for participants who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the participant within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

        i) Confirm if participant has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm electronic diary questionnaires and PROs have been completed and transmitted.

iv) If applicable, confirm participants study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (1).

v) If applicable, remind participant to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: local laboratories may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly and may be captured in the electronic data capture. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Participants may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: the site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

d) Participants may be at risk of potential worsening of diabetic retinopathy with semaglutide.

Mitigation plan: annual retinal examinations will be performed and interpreted by an ophthalmologist or optometrist, as recommended by the American Diabetes Association (ADA) guidelines (ADA Standards of Medical Care in Diabetes Guideline 11.16; ADA 2020; Diabetes Care 2020 Jan; 43 (Supplement 1): S135-S151. https://doi.org/10.2337/dc20-S011).

3) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: if it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should

be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report (CSR). Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

   Mitigation plan: the study monitor is to remain in close communication with the site to ensure data entry and query resolution. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

      Mitigation plan: implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the CSR will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of study drug(s) in study participants remains unchanged.

11.3. Marketing Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in ≥ 1 Country Following EU Regulation No. 536/2014	Authorized in ≥ 1 ICH Country	Authorized by Swissmedic
CILO/FIR	Study drug	No	No	No
SEMA	Study drug	Yes	Yes	Yes

CILO = cilofexor (GS-9674); EU = European Union; FIR = firsocostat (GS-0976); ICH = International Council for Harmonisation; SEMA = semaglutide

11.4. West Haven Criteria

http://www.mdcalc.com/hepatic-encephalopathy-grades-stages/

Grade of Hepatic Encephalopathy	Description	Suggested Operative Criteria
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers
Grade II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least 3 of the following are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms
Grade III	• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least 3 of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms
Grade IV	• Coma	Does not respond even to painful stimuli

Adapted from {Vilstrup 2014}

11.5. Study Procedures Table

	Screening	Day 1	Day 29 (Wk 4) (± 3 d)	Day 57 (Wk 8) (± 3 d)	Day 85 (Wk 12) (± 3 d)	Day 113 (Wk 16) (± 3 d)	Day 169 (Wk 24) (± 3 d)	Day 253 (Wk 36) (± 3 d)	Day 337 (Wk 48) (± 3 d)	Day 421 (Wk 60) (± 3 d)	Day 505 (Wk 72) (−14 d)	ET	Follow -up (± 7 d)[a]
Written informed consent	X												
Confirm eligibility	X	X											
Medical history	X												
Symptom-driven physical examination	X[b]	X	X	X	X	X	X	X	X[b]	X	X[b]	X[b]	X
Assessment of ascites and hepatic encephalopathy[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs including body weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Hip and waist circumference	X	X					X		X		X	X	X
Fundus examination	X[d]								X[d]		X[d]	X[d,e]	
12-lead ECG[f]	X										X	X[e]	
Calculation of the CP and MELD scores	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver biopsy[g]	X										X	X[e]	
Abdominal ultrasound	X						X		X		X	X[h]	
FibroScan®	X						X		X		X	X[h]	
PRO measures		X[i]					X		X		X	X[e]	
Lifestyle counseling	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X	X	X	X			
Review of study drug dosing compliance			X	X	X	X	X	X	X	X	X	X	

	Screening	Day 1	Day 29 (Wk 4) (± 3 d)	Day 57 (Wk 8) (± 3 d)	Day 85 (Wk 12) (± 3 d)	Day 113 (Wk 16) (± 3 d)	Day 169 (Wk 24) (± 3 d)	Day 253 (Wk 36) (± 3 d)	Day 337 (Wk 48) (± 3 d)	Day 421 (Wk 60) (± 3 d)	Day 505 (Wk 72) (−14 d)	ET	Follow -up (± 7 d)[a]
Counseling regarding adherence to study procedures		X	X	X	X	X	X	X	X	X	X		
Participant fasting	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, hematology, and coagulation panels[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Glycemic panel	X	X			X		X		X		X	X	X
Lipid panel	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA_{1c}	X	X			X		X		X		X	X	X
eGFR by MDRD	X	X	X	X	X	X	X	X	X	X	X	X	X
ELF test	X	X			X		X		X		X	X[e]	
SARS-CoV-2 RT-PCR Test[l]	X												
Pregnancy testing[m]	X	X	X	X	X	X	X	X	X	X	X	X	X
Follicle-stimulating hormone[n]	X												
Single PK sampling[o]			X				X		X	X	X	X	
Blood collection (biomarkers)	X	X			X		X		X		X	X[e]	X
Urine collection (biomarkers)	X	X			X		X		X		X	X[e]	X
Stool collection (biomarkers)[p]		X							X		X		
Urine drug screen	X												
HIV-1, HBV, HCV serology	X												

	Screening	Day 1	Day 29 (Wk 4) (± 3 d)	Day 57 (Wk 8) (± 3 d)	Day 85 (Wk 12) (± 3 d)	Day 113 (Wk 16) (± 3 d)	Day 169 (Wk 24) (± 3 d)	Day 253 (Wk 36) (± 3 d)	Day 337 (Wk 48) (± 3 d)	Day 421 (Wk 60) (± 3 d)	Day 505 (Wk 72) (−14 d)	ET	Follow -up (± 7 d)[a]
CCI													

CK = creatinine kinase; COVID-19 = coronavirus disease 2019; CP = Child-Pugh; CTCAE = Common Terminology Criteria for Adverse Events; d = days; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; ET = early termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HbA_{1c} = hemoglobin A_{1c}; HIV-1 = human immunodeficiency virus type 1; MDRD = Modification of Diet in Renal Disease equation; MELD = Model for End-Stage Liver Disease; PK = pharmacokinetic(s); PGIC = Patient Global Impression of Change; PRO = patient-reported outcome; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Wk = week

a Participants will complete a follow-up visit 5 weeks after the Week 72 or ET visit.
b Perform complete physical examination at screening visit only. See Appendix 11.9.1 for France-specific text.
c Assessment is to be done in accordance with established standard practices at the site and if present, graded based on CTCAE or West Haven criteria (Appendix 11.4), respectively.
d For participants with type 2 diabetes diagnosed prior to the date of the screening visit OR based on screening visit $HbA_{1c} \geq 6.5\%$, participants must have no evidence of uncontrolled and potentially unstable retinopathy or maculopathy as determined by a fundoscopic examination performed starting 90 days prior to screening visit date through Day 1. If there has been worsening of the participant's visual function since a historical fundoscopic examination in the opinion of the investigator, then the fundoscopic examination must be repeated prior to Day 1 for eligibility. Pharmacological pupil dilation is a requirement unless using a digital fundus photography camera specified for nondilated examination.
e Assessments to be performed at the discretion of the investigator.
f See Appendix 11.9.1 for France specific text.
g Required for all participants at time of screening unless a qualifying liver biopsy is available per inclusion criterion 3. On-treatment liver biopsy required at Week 72. Early termination liver biopsy at the discretion of the investigator. CCI .
h Assessment to be performed at the ET visit, unless performed within 12 weeks prior to the ET visit.
i PGIC Pain and Fatigue will not be assessed at Day 1.
j Adverse events reporting during screening is limited to SAEs and adverse events related to study procedures.
k If a participant is receiving treatment with both a fibrate and a statin, serum CK should be measured at study visits and appropriate clinical evaluation, including interruption of statin therapy, should be initiated if muscle injury is suspected.
l For participants who have not completed a series of an authorized COVID-19 vaccination regimen prior to screening.
m All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy testing will occur at Day 1 (prior to dosing) and on each treatment visit. Starting at the Week 4 visit, every 4 weeks (± 3 days) urine pregnancy testing may be performed at home in between clinic visits, where possible, or in clinic, if at home pregnancy tests are unavailable.
n Serum FSH test (only for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)
o Single PK sample at Week 4 (15 minutes to 3 hours postdose), Week 24 (anytime postdose), Week 48 (predose), Week 60 (15 minutes to 3 hours postdose), Week 72 (predose), and ET visit (anytime). In cases where the unscheduled visit is performed for the primary purpose of safety evaluation (eg, SAE follow-up), collection of a single PK sample (anytime predose or postdose) is recommended. The timing of the PK sample in relation to the last dose of study drug should be documented. For PK sampling at Weeks 4, 48, 60, and 72, participants should be reminded not to take their oral study drug until advised to do so at their clinic visit.
p Participants will be given a stool sample collection kit at the screening visit and Weeks 36 and 60. Stool sample collection should be completed by the participant in advance of the required study visits (Day 1 and Weeks 48 and 72).
q CCI

11.6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born participant is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for > 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female participant of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born participant is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Participants

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Firsocostat (FIR; GS-0976) and semaglutide (SEMA) are contraindicated in pregnancy as a malformative effect has been demonstrated/suspected or is unknown taking into consideration class effect and/or strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on nonclinical data. Data from clinical pharmacokinetic (PK) interaction studies of FIR, cilofexor (CILO; GS-9674), and SEMA have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception.

Refer to the latest version of the respective investigator's brochures (IBs) and Sections 1.2.2, 1.3.2, and 1.4.2 of the protocol for additional information.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of female participants of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must have a negative serum pregnancy test at screening and a negative pregnancy test at the Day 1 visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter until the end of contraception requirement.

Duration of required contraception for female participants in this clinical study should start from the screening visit until 8 weeks following the last dose of study drug.

Female participants must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Hormonal or nonhormonal intrauterine device
- Subdermal contraceptive implant*
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female participants who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormone-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone*
  - Transdermal contraceptive patch*
  - Contraceptive vaginal ring*
- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide*
  - Cervical cap with spermicide*

— Sponge with spermicide

*Not approved in Japan

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female participants must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female participants should be advised to seek advice about egg donation and cryopreservation of germ cells before treatment.

3) Contraception Requirements for Male Participants

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male participant's seminal fluid and poses a potential risk to an embryo/fetus. Therefore, male participants with female partners of childbearing potential must use condoms during treatment until 8 weeks after last dose of study drug. If the female partner of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Male participants must also refrain from sperm donation during treatment and until the end of contraception requirement.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female participants will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 8 weeks after the last study drug dose. Study drug must be discontinued immediately.

Male participants whose partner has become pregnant or suspects she is pregnant from start of study to 8 weeks after the last study drug dose must also report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

11.7. Lifestyle Recommendations Included in the 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease

1) All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of *trans* fats, red meat and processed red meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss.

2) Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity.

3) For adults with type 2 diabetes, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial.

11.8. Cardiovascular Risk Assessment for Participants With Nonalcoholic Fatty Liver Disease

There are a variety of commonly used cardiovascular disease (CVD) risk calculators that have been developed from studies in different populations. While all of the CVD risk calculators have advantages and disadvantages, no single risk calculator is appropriate for all participants. The choice to use a risk calculator should consider ease of use, applicability to a clinician's participant population, and professional society recommendations.

Some of the most commonly used calculators include:

- United States derived population cohorts:
  - Framingham general CVD risk score, 2008, Circulation. 2008;117:743-753
    - 10-year risk of coronary heart disease (CHD) death, nonfatal myocardial infarction (MI), angina, fatal and nonfatal ischemic/hemorrhagic stroke, transient ischemic attack (TIA), intermittent claudication, heart failure (HF)

    https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/
  - American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort hard CVD risk calculator (2013), Circulation. 2014;129: S49–S73; update Circulation. 2019;140:e596–e646
    - 10-year risk of the following **hard** atherosclerotic cardiovascular disease (ASCVD) events: CHD death, nonfatal MI, fatal and nonfatal stroke

    http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ {American college of Cardiology 2023}
- European derived population cohort
  - SCORE CVD death risk score (2003), Eur Heart J. 2003;24(11):987; Eur Heart J. 2007;28(19):2375. Epub 2007 Aug 28; Eur J Prev Cardiol. 2016 Jul;23(11):NP1-NP96.
    - 10-year risk of CVD death (CHD, arrhythmia, HF, stroke, aortic aneurysm, and peripheral vascular disease)

    https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts
- England and Wales
  - **QRISK and QRISK2:** BMJ. 2007;335(7611):136. Epub 2007 Jul 5, BMJ. 2008;336(7659):1475. Epub 2008 Jun 23.
    - 10-year risk of CHD death, nonfatal MI and stroke, fatal stroke, angina, coronary revascularization, TIA, intermittent claudication

    https://qrisk.org/2017/

11.9. Country-Specific Requirements

11.9.1. Additional Country-Specific Requirements for France

Reflects the changes to the global Amendment 1 protocol dated 25 June 2021 and reflected in Amendment 1.2 (France) dated 23 December 2021.

Country-Specific Requirements	Protocol Section
Ophthalmoscopic examination included as a required component of the complete physical examination.	Section 6.8.2
Study Procedures Table modified to include complete physical examination at Week 48, Week 72, and the early termination visit in addition to Screening.	Appendix 11.5, Section 6.5.2
Study Procedures modified to include electrocardiogram assessments at the Week 24 and Week 48 visits in addition to Screening, Week 72, and the early termination visit.	Synopsis, Appendix 11.5, Section 6.5.2

11.10. Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below, with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing Amendment 1 to this amendment will be made available upon the publication of this protocol.

11.10.1. Amendment 2 (26 October 2023)

Rationale for Key Changes Included in Amendment 2	Affected Sections
Objectives: • Changed the primary objective to evaluate only whether the combination of SEMA with the fixed-dose combination (FDC) of CILO/FIR causes fibrosis improvement without worsening of NASH compared with placebo; NASH resolution is no longer evaluated as part of the primary objective. The rationale for this change is that increasingly fibrosis improvement is recognized as the biomarker most likely to predict clinical benefit in a cirrhotic NASH study population, and this change allows fibrosis improvement to be tested independently as the highest priority hypothesis. • Added a secondary objective to evaluate whether the combination of SEMA with the FDC of CILO/FIR causes NASH resolution in participants with compensated cirrhosis due to NASH, as compared with placebo.	Synopsis, Sections 2 and 8.1.1
Endpoints: • Changed coprimary endpoints to a single primary endpoint of fibrosis improvement without worsening of NASH in order to test fibrosis improvement independently as the highest priority hypothesis, appropriate for a cirrhotic NASH study population. • Information for stastistical testing of the primary and secondary endpoints was changed to order analysis objectives in keeping with the changes to the endpoints, and for consistency with changes made in other sections.	Synopsis, Sections 1.6, 3.1, 8.1.2, 8.2.2, 8.9, and throughout as needed
Estimand strategy was added and updated for primary/secondary endpoints based on the modifications made to the endpoints in the protocol.	Section 8.5
Statistical considerations section was updated to add “power calculation.”	Section 8.9
Dose escalation schedule for SEMA was updated.	Section 5.5.3
Text related to clinical studies of SEMA was updated to add the latest information.	Sections 1.2.3.3, 1.6, and 1.9
Text related to clinical and nonclinical studies of CILO, and FIR (individual and in combination) was updated with the latest information.	Sections 1.3.2, 1.3.3, 1.4.2, 1.4.3, 1.5.2, and 1.9
Clarified that auxiliary medicinal products/noninvestigational medicinal products are not used in this study.	Section 1.10
A list of study interventions and their marketing authorization status was added.	Section 1.10, Appendix 11.3
Added SomaSignal NASH tests to the list of planned biomarkers.	Sections 3.8.1 and 6.8.1.7

Rationale for Key Changes Included in Amendment 2	Affected Sections
Text was updated to add "or other hepatobiliary cancer" to the discontinuation criteria for more clarity.	Section 3.5
CCI [redacted]	Section 3.8.3
Blinding: information was updated regarding personnel who may be unblinded.	Section 5.1.2
The text was updated to add glycyrrhetinic acid to the prohibited medications list: Glycyrrhizae Radix is a traditional herbal medicine commonly prescribed in Japan as an anti-inflammatory agent and contains glycyrrhetinic acid, which confers a mineralocorticoid excess state (sodium retention and potassium wasting). Additional information was provided regarding agents requiring special administration considerations. Azithromycin was moved to agents requiring special administration considerations and noted that chronic use remains prohibited.	Section 5.6
New section regarding definition of serious adverse drug reaction was added.	Section 7.1.3
Section for "Liver-Related Clinical Events" was added.	Section 7.1.4.3
Pregnancy reporting process and time period was updated.	Section 7.4.2.3
The text related to "repeating liver-related laboratory assessments (ALT, AST, ALP, GGT, total bilirubin, INR) within 72 hours of initial results (or as soon as possible)" was removed from toxicity management.	Section 7.7.2
Added text to clarify that laboratory abnormalities that occur before the first dose of study drug or after the participant has been discontinued from treatment for at least 35 days will be included in a data listing.	Section 8.6.3
Clarified that if Gilead discontinues development of the study drug, further provision of study drug to participants may be discontinued.	Section 3.4.1
Clarified that for early termination (ET) visits, a FibroScan assessment should be performed unless performed within 12 weeks of the ET visit.	Section 6.8.10, Appendix 11.5
Clarified that for ET visits, an abdominal ultrasound should be performed unless performed within 12 weeks of the ET visit.	Section 6.8.13, Appendix 11.5
Text was updated to replace "Site Operations Manual" to "Investigator Site File" for alignment with study documents.	Sections 5.1.3, 5.2.2.1, 6.8.11, and 7.2.2
Text was updated to clarify that the urine pregnancy testing may be performed at home in between clinic visits, where possible, or in clinic, if at home pregnancy tests are unavailable.	Section 6.8.8, Appendix 11.5
Text was updated to add visit window of ± 3 days to home pregnancy testing to allow more flexibility.	Section 6.8.8, Appendix 11.5
Contraception requirements were extended from 5 to 8 weeks: contraception requirements updated to specify that acceptable methods of contraception, for both female and male participants, should be continued through 8 weeks after the last dose of study drug due to the long washout period for SEMA, in keeping with guidance from the Warnings and Precautions for Use listed in the SEMA investigator's brochure and labeling for commercially available formulations of SEMA.	Appendix 11.6

Rationale for Key Changes Included in Amendment 2	Affected Sections
Text was added to clarify volume of blood to be collected per participant at each visit and overall.	Section 6.8.1.10
Score description of the Child-Pugh classification of the severity of cirrhosis was updated for clarity.	Section 6.8.5
Text regarding study drug withholding was revised to clarify required observation for participants who discontinue study drug due to evidence of hepatic decompensation.	Section 7.7.3
Added country-specific requirements.	Appendix 11.9
Minor changes to correct typographic errors.	Throughout, as needed

Prot-GS-US-454-6075-amd-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Global Development Lead (GDL) eSigned	26-Oct-2023 23:36:28