CLINICAL STUDY PROTOCOL

Study Title:	A Proof of Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Monotherapy and Combination Regimens in Subjects with Nonalcoholic Steatohepatitis (NASH)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	141683
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT03987074
Indication:	Nonalcoholic steatohepatitis (NASH)
Protocol ID:	GS-US-454-5533

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Protocol Version/Date:	Original:	17 May 2019
	Amendment 1:	16 August 2019
	Amendment 2:	22 October 2019

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

CONFIDENTIALITY STATEMENT

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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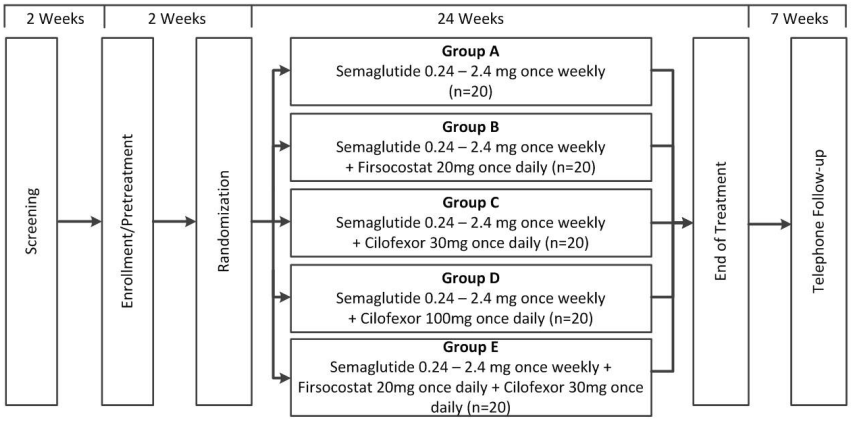
Study Title:	A Proof of Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Monotherapy and Combination Regimens in Subjects with Nonalcoholic Steatohepatitis (NASH)
IND Number:	141683
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT03987074
Study Centers Planned:	Approximately 20 centers in the United States
Objectives:	The primary objective of this study is as follows: • To evaluate the safety and tolerability of study drug(s) in subjects with NASH. CCI [redacted]

Study Design:

This is a proof of concept, open-label study evaluating the safety, tolerability, and efficacy of monotherapy and combination regimens in subjects with NASH.

Subjects meeting the study's entry criteria will be randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 treatment groups, with approximately 20 subjects in each group, as shown in the figure below:



Randomization will be stratified by the presence or absence of type 2 diabetes mellitus, as determined by medical history or based on the Screening laboratory values if previously undiagnosed (hemoglobin A1c [HbA1c] $\geq$ 6.5%).

Number of Subjects Planned: Approximately 100 Subjects

Target Population: Males and non-pregnant, non-lactating females between 18-75 years of age with NASH as assessed by historical liver biopsy, and/or noninvasive tests.

Duration of Treatment: Subjects will be treated for up to 24 weeks

Duration of Study: Participation in the study can last up to 35 weeks, which includes a 2-week Screening period, a 2-week Pre-Treatment period, a 24-week Treatment period, and a 7-week Follow-Up period.

Diagnosis and Main Eligibility Criteria:

Key Inclusion Criteria:

1) Males and females between 18-75 years of age; inclusive based on the date of the Screening Visit;
2) Willing and able to provide informed consent prior to any study specific procedures being performed;
3) Subjects must meet all of the following conditions (a-d) OR (e):
   a. Clinical diagnosis of nonalcoholic fatty liver disease (NAFLD);
   b. Screening FibroTest® < 0.75, unless all previous historical liver biopsies do not reveal cirrhosis. In subjects with Gilbert's syndrome or hemolysis, FibroTest® will be calculated using direct bilirubin instead of total bilirubin;
   c. Screening MRI-PDFF with ≥ 10% steatosis, as assessed by the central reader. Historical MRI-PDFF within 4 weeks of the date of the Screening Visit may be used if deemed acceptable by the central reader;
   d. Screening FibroScan® with liver stiffness ≥ 7 kPa. Historical FibroScan® within 4 weeks of the date of the Screening Visit is acceptable;

   OR

   e. An historical liver biopsy within 6 months of the date of the Screening Visit consistent with NASH (defined as the presence of steatosis, inflammation, and ballooning) with stage 2-3 fibrosis according to the NASH Clinical Research Network (CRN) classification (or equivalent). Report will be reviewed by the Medical Monitor;
4) Subject has the following laboratory parameters at the Screening Visit, as determined by the central laboratory:
   a. Alanine aminotransferase (ALT) ≤ 5 x ULN;
   b. Estimated glomerular filtration rate (eGFR) ≥ 30 milliliter/minute (mL/min), as calculated by the MDRD study equation;
   c. HbA1c ≤ 9.5% (or serum fructosamine ≤ 381 μmol if HbA1c is unable to be resulted);
   d. International normalized ratio (INR) ≤ 1.2, unless due to therapeutic anti-coagulation therapy;
   e. Platelet count ≥ 100,000/μL;
   f. Total bilirubin < 1.3 x ULN unless alternate etiology such as Gilbert's syndrome present;

g. Calcitonin ≤ 100 ng/L;

5) Body Mass Index (BMI) > 23 kg/m^2 and body weight of > 60 kg;

6) A negative serum pregnancy test is required for female subjects of childbearing potential as defined in Appendix 3.

7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.

Key Exclusion Criteria:

1) Documented weight loss > 5% within 6 months of the date of the Screening Visit;

2) Any historical liver biopsy consistent with cirrhosis;

3) Pregnant or lactating females;

4) Alcohol consumption greater than 21 oz/week for males or 14 oz/week for females (1oz/30 mL of alcohol is present in 1 12oz/360 mL beer, 1 4oz/120 mL glass of wine, and a 1oz/30 mL measure of 40% proof alcohol);

5) Positive urine screen for amphetamines, cocaine or opiates (ie, heroin, morphine) at Screening. Subjects on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to the date of Screening Visit may be included in the study. Subjects with a positive urine drug screen due to prescription opioid-based or amphetamine-based medication are eligible if the prescription and diagnosis are reviewed and approved by the investigator;

6) Any history of decompensated liver disease, including ascites, hepatic encephalopathy, or variceal bleeding;

7) Other causes of liver disease, including but not limited to: alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders (eg, primary biliary cholangitis [PBC], primary sclerosing cholangitis [PSC], autoimmune hepatitis), drug-induced hepatotoxicity, Wilson disease, clinically significant iron overload, or alpha-1-antitryspin deficiency requiring treatment;

8) History of liver transplantation;

9) History of hepatocellular carcinoma;

10) Weight reduction surgery in the past 2 years or planned during the study;

11) Chronic hepatitis B (HBsAg positive);

12) Chronic hepatitis C (HCV RNA positive). Subjects cured of HCV infection less than 2 years prior to the date of the Screening Visit are not eligible;

13) HIV Ab positive;

14) Unstable cardiovascular disease as defined by any of the following:

    a. Unstable angina, myocardial infarction, coronary artery bypass graft surgery or coronary angioplasty within 6 months prior to the date of the Screening Visit;

    b. Transient ischemic attack or cerebrovascular accident within 6 months prior to the date of the Screening Visit;

    c. Symptomatic obstructive valvular heart disease or hypertrophic cardiomyopathy;

    d. Symptomatic congestive heart failure;

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

    f. An emergency room visit or hospitalization for confirmed cardiovascular disease within 6 months prior to the date of the Screening Visit;

15) History of a malignancy within 5 years of the date of the Screening Visit with the following exceptions:

    a. Adequately treated carcinoma in situ of the cervix;

    b. Adequately treated basal or squamous cell cancer or other localized non-melanoma skin cancer;

16) Presence of acute pancreatitis within the past 180 days prior to the date of the Screening Visit;

17) History or presence of chronic pancreatitis;

18) Presence or history of type 1 diabetes mellitus;

19) For subjects with type 2 diabetes diagnosed prior to the date of the Screening Visit OR on Screening Visit labs (defined as HbA1c ≥6.5%), subjects must have no evidence of uncontrolled and potentially unstable retinopathy or maculopathy as determined by:

    a. A fundus exam performed in the 90 days prior to the date of the Screening Visit. If there has been worsening of the subject's visual function since this historical fundus exam in the opinion of the investigator, then the fundus exam must be repeated;

    OR

    b. A fundus exam performed between the date of the Screening Visit and Enrollment (Day -14)

    Pharmacological pupil-dilation is a requirement in both of the above cases unless using a digital fundus photography camera specified for non-dilated examination;

20) Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma;

21) Treatment with GLP-1 RAs in the period from 90 days prior to the date of the Screening Visit;

22) Subjects on Vitamin E regimen ≥800 international units (IU)/day must be on a stable dose (defined as no changes in prescribed dose, new Vitamin E containing medications, or discontinuation) for at least 180 days prior to the date of the Screening Visit and in the period between the date of the Screening Visit and Enrollment (Day -14);

23) Subjects on antidiabetic medications must be on a stable dose for at least 90 days prior to the date of the Screening Visit and in the period between the date of the Screening Visit and Enrollment (Day -14);

24) Use of any prohibited concomitant medications as described in Section 5.6;

25) Any investigational medication or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to the date of the Screening Visit throughout the study (e.g., obeticholic acid, elafibranor, and cenicriviroc) is prohibited;

26) Known hypersensitivity to the study drug, the metabolites, or formulation excipient.

Study Procedures/ Frequency:

After signing the informed consent form (ICF), subjects will complete a Screening Visit which will include the following assessments: obtain written informed consent, obtain Screening number from IWRS, complete medical history; if applicable, review of any historical liver biopsy report obtained within 6 months of the date of the Screening Visit; record all concomitant medications that the subject has taken within 30 days prior to Screening; physical examination (PE) including vital signs, body weight, and height; dilated fundus exam or digital fundus photography camera specified for non-dilated examinations (if required for subjects with type 2 diabetes from medical history or from Screening Hemoglobin A1c ≥6.5% only), laboratory assessments, serum pregnancy test (for females of childbearing potential); blood and urine collection for biomarkers, urine drug screen, 12-lead ECG, FibroTest®, ELF™ Test, FibroScan® ; documentation of all serious adverse events (SAEs) and adverse events (AE) related to Screening procedures; MRI-PDFF and MRE examinations.

All subjects determined eligible for the study based on the inclusion/exclusion criteria will then enroll into Pretreatment to begin Cycle 1 of the Kinetic Biomarkers. Subjects will consume deuterated water starting on Day -14 through Day -8 to determine the effects of study drug(s) on kinetic parameters of de novo lipogenesis (DNL), fibrogenesis, and inflammation. The first dose of approximately 45 mL deuterated water will be administered under the supervision of investigative site personnel and monitored for at least 30 minutes after for any side effects. Kinetic biomarker samples will be obtained on Day -14, Day -11, Day -7, and Day 1.

Eligible subjects will be randomized on Day 1 to receive treatment for 24-weeks with one of the following study drugs: semaglutide; firsocostat (FIR; GS-0976) and semaglutide; cilofexor (CILO; GS-9674) and semaglutide; or firsocostat, cilofexor, and semaglutide.

On-treatment study assessments will include but are not limited to:

- Symptom driven PE, vital signs, weight, chemistry, hematology, coagulation panel, and eGFR at Day 1 and at Weeks 1, 4, 8, 12, 16, 20 and 24
- FibroScan®, MRI-PDFF, MRE, and FibroTest® at Weeks 12 and 24
- ELF™ Test at Weeks 12 and 24
- 12-lead ECG at Week 24

- Pregnancy testing (females of childbearing potential only) at Day 1 and at Weeks 4, 8, 12, 16, 20 and 24
- [redacted]
- Insulin and Lipids collection at Day 1, Weeks 4, 8, 12 and 24
- Hemoglobin A1c (HbA1c) collection at Weeks 12 and 24
- Single PK sampling at Weeks 1, 4, 8 and 12
- [redacted]
- Quality of Life (QoL) questionnaires: Chronic Liver Disease Questionnaire-Nonalchoholic Fatty Liver Disease [CLDQ-NAFLD], and EuroQol five dimensions [EQ-5D] at Day 1 and at Weeks 12 and 24

Subjects will return on Day 154 to begin Cycle 2 of the Kinetic Biomarkers. Subjects will drink approximately 45 mL of deuterated water three times per day starting on Day 154 through Day 160. Kinetic biomarker samples will be obtained on Day 154, Day 157, Day 161 and Day 168.

Subjects will complete a Telephone Follow-Up visit 7 weeks after the last dose of study drugs. During this visit, subjects will report on concomitant medications and any adverse events which have occurred since their Week 24 visit. During the Telephone Follow-Up visit, female subjects of childbearing potential that received at least one dose of study drug will report the results of the study-provided urine pregnancy test.

Test Product, Dose, and Mode of Administration:

Name: Semaglutide (0.24 2.4mg)
Dosage form: Solution for injection
Route of administration: Subcutaneous
Dosing instructions: Once weekly
Delivery device: 3 mL PDS290 pre-filled pen-injector

Name: Cilofexor
Dosage form: 30 mg or 100 mg tablet
Route of administration: Oral
Dosing instructions: Once daily

	Name: Firsocostat Dosage form: 20 mg tablet Route of administration: Oral Dosing instructions: Once daily
Dose, and Mode of Administration:	Semaglutide: Dose escalation of semaglutide should take place during the first 16 weeks after randomization. All subjects must aim to reach the recommended target dose of semaglutide subcutaneous (s.c.) 2.4 mg once-weekly. Recommended dose escalation is as follows: • Weeks 1 through 4: 0.24 mg s.c. once weekly • Weeks 5 through 8: 0.5 mg s.c. once weekly • Weeks 9 through 12: 1 mg s.c. once weekly • Weeks 13 through 16: 1.7 mg s.c. once weekly • Weeks 17 through 24: 2.4 mg s.c. once weekly. Cilofexor: One 30 mg or one 100 mg tablet administered orally once daily without regard to food Firsocostat: One 20 mg tablet administered orally once daily without regard to food
Criteria for Evaluation:	
Safety:	Safety will be assessed during the study through the reporting of AEs, and by clinical laboratory tests and vital sign assessments at various time points during the study. Concomitant medication usage will also be assessed throughout the study.
Pharmacokinetics:	The PK of study drug(s) and relevant metabolite(s) may be evaluated, as applicable. PK samples may also be used to measure protein-binding of study drug(s) and/or its metabolites. Plasma concentrations of study drug(s) will be provided in a listing.
Statistical Methods:	
Primary Endpoint:	The primary endpoint is the safety and tolerability of study drug(s) in subjects with NASH.

CCI [redacted]

Efficacy Analysis: The biological activity of study drug(s) will be evaluated using radiologic endpoints and biomarker variables. Because efficacy endpoints will be evaluated for exploratory purposes, formal statistical comparisons will not be made for these endpoints. Instead, descriptive statistics (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, and maximum) will be provided by treatment group.

CCI [redacted]

Safety Analysis:	Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous values by treatment group.
Pharmacokinetic Analysis:	Plasma concentrations of study drug(s) and relevant metabolite(s), as applicable, will be listed.
Kinetic Biomarker Analysis:	The kinetic biomarkers will be analyzed to evaluate the pharmacodynamic (PD) effects of study drug(s). The assessment will involve the analysis of DNL values; specifically, the change (absolute and relative) from baseline between the post-dose and pre-dose deuterated water loading periods.
Sample Size:	Due to the exploratory nature of this study, the sample size was not determined by any formal power calculation. The number of subjects in each treatment group was decided based on clinical experience with other similar proof of concept studies.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ACC	acetyl-CoA carboxylase
AE	adverse event
AICD	automatic implantable cardioverter defibrillator
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma/serum concentration versus time curve
$AUC_{2\text{-}12hr}$	partial area under the plasma/serum concentration versus time curve from time 2 to time 12
AUC_{24hr}	area under the plasma/serum concentration versus time curve from time zero to time 24
AUC_{inf}	area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\ last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
BAP	Biomarker Analysis Plan
BCRP	breast cancer resistance protein
BMI	body mass index
BUN	blood urea nitrogen
CAP	controlled attenuation parameter
CFR	Code of Federal Regulations
CI	confidence interval
C_{last}	last observed quantifiable plasma/serum concentration of the drug
CLDQ-NAFLD	Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease
C_{max}	maximum observed plasma/serum concentration of drug
CP	Child-Pugh
CPK	creatine phosphokinase
CRN	Clinical Research Network
CRO	contract research organization
CRP	c-reactive protein
CsA	single dose cyclosporine
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
CYP3A	cytochrome P4503 A
CYP3A4	cytochrome P4503 A4
CYP7A1	cytochrome P450 7A1
DDI	drug-drug interaction
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee

DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
DRSP	Drospirenone
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eg	Example
eGFR	estimated glomerular filtration rate
ELF™	Enhanced Liver Fibrosis
EQ-5D	EuroQol five dimensions
F2	Moderate Fibrosis
F3	Bridging Fibrosis
F4	Compensated Cirrhosis
FDA	(United States) Food and Drug Administration
FFD	Fast food diet
FGF19	fibroblast growth factor 19
FSH	follicle stimulating hormone
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GMR	geometric mean ratio
GSI	Gilead Sciences, Inc.
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	Hepatocellular Carcinoma
Hct	Hematocrit
HCV	hepatitis c virus
HCV Ab	hepatitis c virus antibody
HCV RNA	hepatitis c virus ribonucleic acid
HDPE	high-density polyethylene
HE	hepatic encephalopathy
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HIV Ab	human immunodeficiency virus antibody
HIV RNA	human immunodeficiency virus ribonucleic acid
HLGT	high-level group term

HLT	high-level term
HOMA-IR	homeostatic assessment of insulin resistance
HR	hazard ratio
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	institutional review board
IU	international units
IUD	intrauterine device
IV	Intravenous
IWRS	Interactive web response system
kg	Kilogram
kPa	Kilopascal
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LEAN	**L**iraglutide **E**fficacy and **A**ction in **N**ASH
LLT	lower-level term
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MD	multiple dose
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	millimeter of Mercury
MRE	magnetic resonance elastography
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
MRP2	multidrug resistance-associated protein 2
N	Number
NAFLD	nonalcoholic fatty liver disease
$NaNO_2$	sodium nitrite
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NOAEL	no observed adverse event level

NTCP	sodium-taurocholate cotransporting polypeptide
OATP	organic anion-transporting polypeptide
OAD	oral antidiabetic drug
OL	Open-Label
PBC	primary biliary cholangitis / probenecid
PD	pharmacodynamic
PDGF	platelet-derived growth factor
PE	physical exam
P-gp	Permeability-glycoprotein
PIIINP	procollagen III amino terminal peptide
PK	pharmacokinetic
PRO	patient-reported outcomes
PSC	primary sclerosing cholangitis
PT	prothrombin time / Preferred Term
PTT	partial thromboplastin time
PVE	Pharmacovigilance & Epidemiology
QD	once daily
QTc	QT interval corrected for heart rate
RBC	red blood cell count
RIF	Rifampin
RNA	ribonucleic acid
ROS	reactive oxygen species
SADR	serious adverse drug reaction
SAE	serious adverse event
s.c.	subcutaneous
SD	standard deviation
SD	single dose
SEMA	Semaglutide
SOC	System Organ Class
SOP	standard operating procedure
SREBP-1c	sterol regulatory element binding protein-1c
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
T2D	type 2 diabetes
TIMP-1	tissue inhibitor of metalloproteinase 1
T_{max}	time (observed time point) of C_{max}
UGT	UDP-glucuronosyltransferase
ULN	upper limit of the normal range
US	United States

VAS	Visual Analog Scale
VLDL	very-large density lipoprotein
VORI	Voriconazole
WBC	white blood cell count

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 diabetes mellitus 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 ranges from 6% to 37% worldwide {Ong 2007, Vernon 2011} with a recent reported pooled global prevalence of 25% {Younossi 2016}.

Nonalcoholic steatohepatitis (NASH), an aggressive form of NAFLD 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 ~15 million adults, have NASH. Furthermore, as NASH is a manifestation of the metabolic syndrome, risk factors for cardiovascular disease frequently coexist in these patients {Dietrich 2014, Faramawi 2008, Voulgari 2010}. Given the absence of any approved therapies and the increasing prevalence of NASH co-morbidities, NASH is expected to represent an increasingly large unmet medical need.

As noted previously, NASH is primarily thought to occur as the result of the metabolic syndrome: the impact of obesity, insulin resistance, and dyslipidemia. Fatty liver, or simple steatosis is not sufficient to cause liver injury. Rather, it is the presence of inflammation and hepatocellular injury on the background of steatosis that defines NASH and may result in the progression to cirrhosis and its complications. The “2-hit” hypothesis of NASH suggests that in the setting of steatosis and metabolic dysfunction, increased oxidative stress and the generation of reactive oxygen species (ROS) likely mediate the inflammatory changes in the liver (steatohepatitis) that may lead to progressive fibrosis {Dowman 2010, Koek 2011, Sumida 2013}. The major pathways in NASH disease progression include those involved in metabolic dysfunction in the hepatocyte, and activation of hepatic stellate cells and macrophages leading to progressive inflammation and liver fibrosis. Advanced fibrosis and cirrhosis are characterized by extensive collagen deposition and remodeling of the extracellular matrix. Additionally, evidence suggests that lipotoxic intermediates of fatty acids likely contribute to the etiology of NASH {Neuschwander-Tetri 2010}.

Over time, NASH may result in progressive liver fibrosis, ultimately leading to cirrhosis in 10-20% of affected patients. Advanced fibrosis (bridging fibrosis or cirrhosis) 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. Decompensated liver disease, as defined by the development of one of the above complications, has a high mortality and the only known effective treatment is liver transplantation. With the increasing prevalence of obesity and obesity-related diseases, NASH is expected to become the leading indication for liver transplantation and the leading etiology of HCC among liver transplant recipients in the US {Afzali 2012, Wong 2014}.

1.2. General Information for Semaglutide

1.2.1. General Information

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) currently in development for weight management and non-alcoholic steatohepatitis. Semaglutide at once weekly doses of 0.5 mg and 1.0 mg has been approved as an adjunct to diet and exercise for the management of Type 2 diabetes 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 semaglutide molecule is primarily obtained by increased albumin binding, which is facilitated by a large fatty acid-derived chemical moiety.

Please refer to the Investigator's Brochure (IB) for additional information on semaglutide, including:

- In vitro activity
- Nonclinical in vivo efficacy studies
- Nonclinical pharmacokinetics and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical pharmacokinetics and pharmacodynamics
- Safety in healthy subjects, subjects with obesity and subjects with type 2 diabetes (T2D)

1.2.2. Pre-Clinical Studies

Nonclinical efficacy data have shown that semaglutide lowers blood glucose, food intake and body weight in animal models of diabetes and obesity. Furthermore, semaglutide attenuated the development of atherosclerosis and had an anti-inflammatory action in the cardiovascular (CV) system. 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 duration, respectively. In all three 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 semaglutide. Non-lethal thyroid C-cell tumours observed in rodents are a class effect for the GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. The C-cell changes in rodents are caused by a nongenotoxic, 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 to be low, but cannot be completely excluded.

Semaglutide adversely affected embryo fetal 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 foetal 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.

Refer to the Semaglutide IB for additional details.

1.2.3. Clinical Trials with Semaglutide

As part of the T2D development program, semaglutide once weekly was evaluated in 9 Phase 3a/b trials (including a 2-year cardiovascular outcomes trial [CVOT]). Across all Phase 3a/b efficacy trials, both semaglutide 0.5 mg and 1.0 mg were superior in lowering glycosylated hemoglobin (HbA1c) and body weight as compared with placebo (both as monotherapy and in combination with insulin) or compared with the respective marketed comparators. CV safety of semaglutide was established in the CVOT with an estimated hazard ratio (HR) for semaglutide vs. placebo of 0.74 [0.58; 0.95] 95%CI corresponding to a reduced risk of major adverse cardiovascular events (MACE) by 26% vs. placebo.

The PK and PD properties of semaglutide s.c. administered once weekly was investigated as part of the T2D development program including a total of 16 clinical pharmacology trials. Semaglutide has PK properties compatible with once-weekly administration with a median time to maximum concentration (tmax) of 1-3 days and an elimination half-life (t½) of approximately 1 week. The exposure of semaglutide in subjects with various degrees of impaired renal function and with various degrees of impaired hepatic function was similar to the exposure in subjects with normal renal function and normal hepatic function, respectively. No clinically relevant drug-drug interactions (DDIs) were observed between semaglutide 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 drugs are required. Semaglutide circulates in plasma, highly bound to plasma protein. Prior to excretion, semaglutide is metabolized and excreted in urine and feces, with only 3% of the administered dose excreted as intact semaglutide.

For the evaluation of semaglutide in weight loss, Novo Nordisk A/S has conducted one phase 2 clinical dose finding trial of semaglutide s.c. treatment in subjects with obesity. 857 eligible subjects were randomised to a target daily dose of semaglutide 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg, liraglutide 3.0 mg or corresponding placebo matching each of the active treatment arms. Overall, a dose-dependent decrease in body weight was observed from baseline at week 52, with the greatest weight loss (estimated mean change in body weight -13.84%) observed with the highest semaglutide dose tested (0.4 mg, once daily). Weight loss was accompanied by consistent improvements in weight-related comorbidities, such as CV risk factors as well as in patient-reported outcomes (PRO). No unexpected safety findings were identified and the tolerability and safety profile was overall consistent with previous findings in the semaglutide s.c. development program for T2D and the GLP-1 RA class in general. The most frequently reported AEs were gastrointestinal (GI) disorders (mainly nausea).

Semaglutide did not increase the risk of severe or blood glucose (BG) confirmed symptomatic hypoglycemia when used as monotherapy or in combination with oral antidiabetic drugs (OADs) (excluding sulphonylurea), and only slightly increased the risk when used in combination with insulin and with sulphonylurea.

Allergic reactions and injection site reactions were generally infrequent, non-serious and of mild or moderate severity and reported by a similar proportion of subjects on semaglutide and placebo and comparator products (allergic reactions: 4 6%) and (injection site reactions ~1%).

Data from the CVOT in T2D showed that semaglutide treatment was associated with an increased risk of diabetic retinopathy complications in subjects with pre-existing diabetic retinopathy, albeit at low risk. This finding is believed to be attributable to the rapid initial improvement in BG levels with semaglutide, consistent with the early worsening phenomenon described with insulins. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines.

No causal association between semaglutide and any type of neoplasms has been seen in the clinical development program. The incidence of pancreatic cancer and breast neoplasms was low and appeared not to be different from placebo or other comparators.

1.3. General Information for Cilofexor

1.3.1. Cilofexor

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. Thus cilofexor, by agonizing FXR, is expected to improve NASH. Please refer to the Investigator's Brochure (IB) for additional information on cilofexor, including:

- In vitro FXR agonism
- Nonclinical in vivo efficacy studies
- Nonclinical pharmacokinetics and in vitro metabolism
- Nonclinical pharmacology and toxicology

1.3.2. Nonclinical Pharmacology and Toxicology

In vivo pharmacology studies have demonstrated that cilofexor preferentially activates intestinal FXR and reduces liver fibrosis. In cynomolgus monkeys, there was an increase in circulating FGF19 levels after oral dosing of cilofexor but not after IV dosing despite greater exposure to cilofexor after IV dosing. These data suggest that intestinal FXR agonism by cilofexor causes FGF19 production, whereas low systemic free drug concentrations limit effects following IV administration of cilofexor. In addition, the oral administration of cilofexor to monkeys directly activated intestinal FXR, as measured by the expression of FXR-target genes in the ileum (FGF19, OSTα, and OSTβ mRNA). In a mouse model of NASH induced by a diet enriched in fat, cholesterol and sugar, cilofexor reduced hepatic steatosis and normalized bile acid levels in plasma. In a choline-deficient high fat diet /NaNO2 rat model of liver fibrosis that utilizes "2 hits" to mimic the metabolic and oxidative stress components of NASH in humans, cilofexor dose dependently reduced both biochemical and histological measures of liver fibrosis. Overall, the results from these pharmacology studies demonstrate that cilofexor is a potent and selective agonist of intestinal FXR with the potential to benefit NASH patients by inducing FGF19 production.

The oral bioavailability of cilofexor was low in the nonclinical species. cilofexor was extensively bound to plasma proteins in all species. In mice, [^{14}C] cilofexor-derived radioactivity was distributed to most of the tissues, with the highest maximum concentrations of radioactivity determined in organs of absorption and excretion. No quantifiable radioactivity was detected in brain, suggesting [^{14}C] cilofexor-derived radioactivity did not cross the blood: brain barrier. The primary cilofexor metabolic pathways in pooled cryopreserved hepatocytes were observed to be oxidative. Comparison of metabolism in hepatocytes from mice, rats, dogs, monkeys, and humans did not identify any metabolites unique to humans. The primary metabolic pathways of [^{14}C] Cilofexor in vivo were oxidation and *O*-dealkylation in mice, rats, and monkeys; glutathione conjugation was observed in mice and rats; additionally, dechlorination was observed

in mice. Fecal elimination was a predominant route of elimination of [^{14}C] cilofexor-derived radioactivity in both mice and monkeys.

Based on nonclinical assays, cilofexor has the potential to affect hepatic/intestinal uptake of organic anion-transporting polypeptide (OATP) substrates or metabolism of CYP2C8, CYP2C9, or CYP3A4 substrates when its concentrations are sufficiently high. However, low solubility, high protein binding (> 99.98%), and low systemic levels reduce the potential for cilofexor to cause drug-drug interactions (DDIs) via inhibition of metabolic enzymes and transporters. GS-716070, an inactive metabolite of cilofexor, was found to inhibit human OATP1B1, OATP1B3, and OATP2B1 with IC_{50} values of 0.94, 1.3, and 2.5 μM, respectively.

Cilofexor was a substrate for efflux transporters P-gp and breast cancer resistance protein (BCRP), as well as the uptake transporters OATP1B1, OATP1B3, OATP2B1, and sodium-taurocholate cotransporting polypeptide (NTCP). Inhibitors or genetic polymorphisms affecting the activity of these transporters may affect cilofexor intestinal absorption and hepatic uptake.

Cilofexor and GS-716070 did not activate nuclear hormone receptors associated with the potential for induction of human drug-metabolizing enzymes and transporters (eg, PXR, CAR, AhR) in cell-based reporter assays. Thus, the liability of cilofexor and GS-716070 to cause DDIs through proteins regulated by these nuclear receptors is low.

Based on nonclinical assays, GS-1056756 (the R-enantiomer of M13), an inactive, major circulating metabolite of cilofexor has shown low potential to inhibit CYP enzymes (IC_{50} values of 3.49 for CYP2C8 and >25 uM for CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6) and UDP-glucuronosyltransferase (UGT) (IC_{50} value of 13.9 for UGT1A1) in vivo. GS-1056756 did not inhibit P-gp, BCRP, OCT2, MATE1, MATE2K, and showed low probability to be clinically relevant inhibitor of OAT1, OCT1, OATP1B1, OATP1B3 or OATP2B1. No clinical DDI liability of GS-1056756 on enzymes and transporters was predicted from in vitro characterizations.

GS-1056756 has been identified in nonclinical assays as a substrate of OATP1B1/1B3. In vitro, GS-1056756 is formed by oxidative metabolism by CYP3A4 and CYP2C8 with additional conversion to enantiomers by dehydrogenases (eg, ALDH), and is subsequently metabolized by CYP3A and CYP2C8 and UGTs. Together with available clinical data described in Section 1.3.3, the potential clinical DDI liability of GS-1056756 is low.

The nonclinical toxicity profile of cilofexor has been assessed in mice and cynomolgus monkeys administered cilofexor orally for up to 26 and 39 weeks, respectively. Findings attributed to cilofexor administration were primarily related to the liver (increases in alkaline phosphatase, decreases in serum bile acids, cholesterol and triglycerides, increases in liver weight and hepatocellular hypertrophy) and were likely related to the pharmacology of cilofexor. These findings were minimal to mild, non-adverse, and reversible after discontinuation of treatment. The no observed adverse event levels (NOAELs) after 26 and 39 weeks of dosing in mice and monkeys, respectively, were associated with exposures (AUC_{24h}) that were 22- and 32-fold higher in mice and monkeys, respectively, than the observed exposure in humans administered 100 mg cilofexor QD with food.

1.3.3. Clinical Trials of Cilofexor

As of 2 August 2018, 4 Phase 1 clinical studies are complete, 2 Phase 1 studies are ongoing (GS-US-402-3885 and GS-US-402-4287), 1 Phase 2 study in subjects with NASH is complete (GS-US-402-1852) and 4 Phase 2 studies in subjects with NASH (GS-US-384-3914, GS-US-454-4378), Primary Biliary Cholangitis (PBC) (GS-US-427-4024), and PSC (GS-US-428-4025) are ongoing. These Phase 1 and 2 studies are described in the IB. A brief summary of relevant PK results supporting this protocol is presented below, including preliminary results that are not included in the IB from ongoing study GS-US-402-3885 and GS-US-428-4025. Preliminary clinical PK data for the newly identified major circulating cilofexor metabolite GS-1056756 (the R-enantiomer of M13) is described in Sections 1.3.4.3. Briefly, GS-1056756 exhibits a plasma half-life of approximately 175 h. Preliminary steady-state plasma concentrations of GS-1056756 in PSC patients administered 100 mg cilofexor are as expected based on the preliminary single dose PK data for GS-1056756 from the ADME study (GS-US-402-4287). Additionally, plasma exposures of GS-1056756 are minimally altered in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. These data, taken together with the adequate safety margins from nonclinical safety studies and the nonclinical understanding of the metabolic formation (CYP3A and CYP2C8) and clearance (CYP3A, CYP2C8, and UGTs) mechanisms of GS-1056756 support the concomitant medication restrictions in Section 5.3.

1.3.4. A Phase 1, Open-Label, Parallel-Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics and Pharmacodynamics of Cilofexor in Subjects with Normal and Impaired Hepatic Function (Study GS-US-402-3885)

Study GS-US-402-3885 is an ongoing Phase 1, open-label, parallel-group, single dose study evaluating the safety, tolerability, PK, and PD of cilofexor in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment. Up to 60 subjects are planned for enrollment in 1 of 3 hepatic impairment cohorts: Cohort 1 (mild hepatic impairment, CP A), Cohort 2 (moderate hepatic impairment, CP B), and Cohort 3 (severe hepatic impairment, CP C). Within each cohort, each subject with impaired hepatic function (N 10 per cohort) will be matched for age (± 10 years), sex, race, and body mass index (BMI: ± 15%) with a control subject with normal hepatic function (N 10 per cohort). Data from healthy subjects may be used in >1 cohort if a subject was an appropriate match for a subject with hepatic function in >1 cohort. All subjects in Cohorts 1 and 2 will receive a single oral dose of cilofexor 30 mg in the fed state on Day 1 with PD collected on Day -1 and Day 1. All subjects in Cohort 3 will receive a single oral dose of cilofexor 10 mg in the fed state on Day 1 with PD collected on Day -1 and Day 1.

1.3.4.1. Subject Disposition

As of 1 November 2017 a total of 37 subjects were enrolled and 36 subjects had completed study treatment. One subject prematurely discontinued study treatment due to quality issues at the site that justified a suspension in dosing at the site. No subjects prematurely discontinued due to an adverse event (AE), withdrew consent, or were lost to follow-up.

1.3.4.2. Preliminary Safety Results

Overall, 8.8% of subjects had a treatment-emergent adverse event (TEAE) of Grade 1 or 2. There was 1 serious adverse event (SAE) of gastrointestinal bleed that was not related to study drug. This subject had a history of esophageal variceal bleeding and experienced bleeding requiring hospitalization and blood transfusion. There were no pregnancies or deaths.

In the mild hepatic impairment cohort, there were 2 subjects (20%) that had Grade 3 lab abnormalities of elevated gamma glutamyl transferase (GGT) and low platelets. The Grade 3 GGT was stable from the subject's baseline. There was 1 healthy matched control subject (10%) who had Grade 3 lab abnormalities in total cholesterol and LDL cholesterol (LDL-C), which were stable from their baseline. In the moderate hepatic impairment cohort, 2 subjects (20%) had Grade 3 lab abnormalities. One subject had low lymphocytes, and the other subject had elevated total bilirubin and low platelets. The platelet count was not changed from the subject's baseline. One subject, who had a SAE of gastrointestinal bleeding in the moderate hepatic impairment cohort (described above), had a Grade 4 lab abnormality of low hemoglobin. In the severe hepatic impairment cohort, 4 subjects (40%) had greater than or equal to Grade 3 lab abnormalities at baseline. One subject had low hemoglobin, one subject had elevated total bilirubin, one subject had low hemoglobin and low albumin, and one subject had occult blood in urine.

1.3.4.3. Preliminary PK Results

Preliminary PK results are presented below and in Table 1-1:

- Cohort 1 (mild hepatic impairment; CP A): cilofexor exposure (AUC_{inf} and C_{max}) was higher in subjects with mild hepatic impairment (approximately 76% and 57%, respectively) as compared to subjects with normal hepatic function. In subjects with mild hepatic impairment, exposure (AUC_{inf} and C_{max}) of the metabolite GS-716070 was similarly higher (approximately 64% and 25%, respectively). Overall exposure for GS-1056756 was modestly higher (AUC_{inf} was increased 28% and C_{max} increased 7%) in subjects with mild hepatic impairment compared with subjects with normal hepatic function. cilofexor and GS-716070 had minor changes in plasma protein binding (unbound fraction [f_u] increased ~30%). CILO is a hepatic OATP substrate and OATP expression/activity may be altered in patients with cirrhosis. Thus, altered OATP expression/activity may contribute to the observed higher systemic exposure of cilofexor. At a dose of 100 mg QD in subjects with mild hepatic impairment, exposure margins relative to preclinical NOAEL exposures for both parent and metabolites are expected to remain adequate.

- Cohort 2 (moderate hepatic impairment; CP B): CILO exposure (AUC_{inf} and C_{max}) was higher in subjects with moderate hepatic impairment (approximately 2.3- and 1.6-fold, respectively) as compared to subjects with normal hepatic function. Exposure (AUC_{inf}) of the metabolite GS-716070 was also higher (approximately 1.6-fold) with minimal change in C_{max}. GS-1056756 AUC_{inf} was increased 16% and C_{max} was 30% lower in subjects with moderate hepatic impairment compared with subjects with normal hepatic function. Plasma unbound fraction (f_u) of cilofexor and GS-716070 was increased ~96% and ~85%, respectively, in moderate hepatic impairment, leading to a > 4-fold and > 3-fold increase in free drug exposures of parent and metabolites, respectively.

- Cohort 3 (severe hepatic impairment; CP C): cilofexor exposure (AUC_{inf} and C_{max}) was higher in subjects with severe hepatic impairment (approximately 6.2- and 2.5-fold, respectively) as compared to subjects with normal hepatic function. Exposure (AUC_{inf}) of the metabolite GS-716070 was also higher (approximately 3-fold) with C_{max} reduced by 33%. GS-1056756 AUC_{inf} was approximately 2.6-fold higher and C_{max} approximately 39% lower in subjects with severe hepatic impairment compared with subjects with normal hepatic function.

Table 1-1. GS-US-402-3885: Preliminary Cilofexor, GS-716070, and GS-1056756 PK Parameters Following a Single Dose of Cilofexor 30 mg or 10 mg in Subjects with Hepatic Impairment or Normal Hepatic Function

Cohort	Analyte	Mean (%CV) PK Parameter	Matched Healthy Control (N=10)	Hepatic Impairment (N=10)	%GMR (90% CI)
1 (Mild HI, CILO 30 mg)	Cilofexor	AUC_{inf} (hr.ng/mL)	3030 (40.5)	5410 (40.2)	176 (127, 253)
		AUC_{last} (hr.ng/mL)	2970 (41.4)	5380 (40.4)	178 (128, 247)
		C_{max} (ng/mL)	604 (45.6)	994 (53.7)	157 (108, 229)
	GS-716070	AUC_{inf} (hr.ng/mL)	1440 (49.7)	2330 (44.8)	164 (104, 259)
		AUC_{last} (hr.ng/mL)	1400 (51.1)	2300 (44.8)	169 (115, 247)
		C_{max} (ng/mL)	179 (42.6)	234 (50.8)	125 (85.0, 188)
	GS-1056756	AUC_{inf} (hr.ng/mL)	2040 (57.7)	2850 (69.5)	128 (80.1, 204)
		AUC_{last} (hr.ng/mL)	850 (45.6)	1030 (70.0)	109 (73.0, 163)
		C_{max} (ng/mL)	13.0 (44.4)	15.5 (70.1)	107 (70.4-161)
2 (Moderate HI, CILO 30 mg)	Cilofexor	AUC_{inf} (hr.ng/mL)	2810 (30.3)	8280 (91.4)	230 (163, 324)
		AUC_{last} (hr.ng/mL)	2460 (30.9)	8220 (91.1)	249 (169, 367)
		C_{max} (ng/mL)	496 (40.2)	909 (52.5)	164 (115, 233)
	GS-716070	AUC_{inf} (hr.ng/mL)	1380 (47.7)	3160 (81.8)	163 (95.1, 280)
		AUC_{last} (hr.ng/mL)	1340 (48.8)	3090 (80.9)	197 (117, 329)
		C_{max} (ng/mL)	168 (51.6)	181 (61.5)	89.5 (54.3, 147)
	GS-1056756	AUC_{inf} (hr.ng/mL)	1620 (41.6)	1900 (41.2)	116 (83.5-161)
		AUC_{last} (hr.ng/mL)	734 (40.7)	586 (34)	79.4 (58.3, 108)
		C_{max} (ng/mL)	11.6 (39.7)	8.25 (37.6)	70.0 (50.2, 97.6)

Cohort	Analyte	Mean (%CV) PK Parameter	Matched Healthy Control (N=10)	Hepatic Impairment (N=10)	%GMR (90% CI)
3 (Severe HI, CILO 10 mg)	Cilofexor	AUC_{inf} (hr.ng/mL)	989 (36.4)	6710 (60.3)	623 (430, 905)
		AUC_{last} (hr.ng/mL)	963 (37.2)	6535 (58.0)	631 (437, 913)
		C_{max} (ng/mL)	182 (47.5)	427 (32.0)	254 (177, 365)
	GS-716070	AUC_{inf} (hr.ng/mL)	2450 (77.5)	688 (50.1)	303 (173, 528)
		AUC_{last} (hr.ng/mL)	2070 (71.2)	653 (52.9)	280 (166, 473)
		C_{max} (ng/mL)	47.9 (45.6)	77.2 (55.7)	67.0 (44.3-101)
	GS-1056756	AUC_{inf} (hr.ng/mL)	520 (38.8)	3360 (181)	262 (118, 581)
		AUC_{last} (hr.ng/mL)	241 (39.2)	181 (45.8)	73 (51.0, 104)
		C_{max} (ng/mL)	3.67 (37.0)	2.35 (50.2)	60.7 (41.9, 88.0)

Data reported to 3 significant figures

- Preliminary PD results for Cohort 1 are also available for change from baseline (Day -1) in plasma FGF19 and serum 7-alpha-hydroxy-4-cholesten-3-one (C4) levels following a single 30-mg dose of cilofexor. Changes in FGF19 and C4 following a single dose of cilofexor were similar in the mild hepatic impairment subjects as compared to the healthy matched controls as indicated by the PD parameter ratios (mild hepatic impairment/healthy) for C_{max} and $AUC_{2\ 12hr}$ for FGF19 (1.1 and 1.1, respectively) and for C_{min} and $AUC_{2\ 12hr}$ for C4 (0.82 and 0.87, respectively) that were not significantly different from 1.

- Based on the preliminary PK and PD data from this study as well as the overall safety profile of cilofexor, dose adjustments are not considered necessary in subjects with mild hepatic impairment.

- For further information on cilofexor, refer to the current IB.

1.4. General Information for Firsocostat

1.4.1. Firsocostat

Firsocostat is a small molecule allosteric inhibitor that acts at the protein-protein homodimer interface of acetyl coenzyme A (acetyl-CoA) carboxylases (ACC) ACC1 and ACC2 to prevent dimerization. ACC1 and ACC2 are important regulators of fatty acid metabolism. ACC1 catalyzes the first step of de novo lipogenesis (DNL) by converting acetyl-CoA to malonyl-CoA 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. Firsocostat is being developed for the treatment of nonalcoholic steatohepatitis (NASH) under IND 124915.

For further information on firsocostat, refer to the current IB.

1.4.2. Nonclinical Pharmacology

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

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

As described in the IB, GS-834356, a liver-targeted ACC inhibitor and analogue of firsocostat, reduced steatosis in a murine model of NASH induced by a diet enriched in fat, cholesterol, and fructose (Fast food diet, FFD). ACC inhibition by GS-834356 dose-dependently reduced hepatic steatosis, liver triglycerides and cholesterol, plasma ALT and AST, and markers of hepatic fibrosis, but also dose-dependently increased plasma triglycerides in this model. 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, Hertz 1995, Kim 2017}.

In high fat, high sucrose fed rats, GS-834356-induced increased plasma triglycerides were found to be due to increased very-large density lipoprotein (VLDL) secretion and decreased clearance of triglyceride-rich VLDL and chylomicrons[2]. The increase in plasma triglycerides by ACC inhibition was accompanied by an increase in plasma ApoC3 protein, which inhibits lipoprotein lipase activity and suppresses VLDL and chylomicron clearance. ApoC3 transcription in hepatocytes is repressed by the nuclear hormone receptor PPARα[3]. Evaluation of gene transcription profiles of FFD-fed mice treated with the ACC inhibitor GS-834356 revealed a reduction in PPARα target gene signatures[2].These findings suggest that ACC inhibition in the liver leads to a reduction in hepatic PPARα activity and associated increases in VLDL and ApoC3 production, and reduced VLDL/chylomicron clearance. Indeed, the combination of ACC

inhibition with PPARα agonism using fenofibrate blocked the ACC-induced plasma TG increases in the mouse NASH model. Importantly, the combination of the ACC inhibitor and fenofibrate caused a similar reduction in hepatic triglycerides compared to ACC inhibitor treatment alone. In addition, the combination caused a greater increase in plasma ketone bodies (a marker of fatty acid beta-oxidation) and a greater reduction of hepatic cholesterol levels relative to ACC inhibition alone[2]. These findings demonstrate that the addition of fenofibrate overcomes triglyceride elevations induced by ACC inhibition and further increases fatty acid oxidation and cholesterol metabolism.

In total, these studies confirm the potential for firsocostat to impact important metabolic endpoints associated with NASH, and for the addition of PPARα agonists to reverse increases in plasma triglycerides.

Please refer to the firsocostat IB for additional details.

1.4.3. Nonclinical Toxicology

The nonclinical toxicologic profile of firsocostat has been well characterized in single- and repeat-dose toxicity studies up to 39 weeks in duration and in genetic toxicity, embryo-fetal developmental toxicity, and local tolerance studies.

Firsocostat was well tolerated up to 13 weeks in the mouse, 26 weeks in the rat, and 39 weeks in the dog. The primary target organ toxicity was the presence of cataracts and/or lens degeneration in the mouse and dog after 2 and 13 weeks, respectively. In the 2-week mouse study, while 1 of 10 female mice at the lowest dose (5 mg/kg/day) had lens degeneration, none of the male mice at the same dose, whereas they did at 3 times higher mean firsocostat exposure. In the females, the lowest exposure where lens degeneration was observed was 5 times higher than the clinical exposure at 20 mg firsocostat.

In contrast, in the 13-week mouse study, there were no eye findings that were attributed to firsocostat exposures approximately 8-fold above the clinical exposure at 20 mg. While the relevance of the lens degeneration observed in the mouse to humans is currently unknown, the lack of eye findings attributable to firsocostat in the 13-week mouse study and the differences in the eye anatomy between mouse and human suggest that eye findings at lower exposures in the 2-week study may not be clinically relevant. In the dog, lens degeneration/cataracts were first observed after 13 weeks of firsocostat administration. While lens degeneration/cataracts were also observed in the chronic dog study, these findings occurred at exposures > 168 times the clinical exposure at 20 mg.

There were no adverse eye findings in the chronic dog study at mean exposures at least 48 times the clinical exposure at 20 mg. firsocostat was not genotoxic and there was no embryo-fetal developmental toxicity at exposures approximately 50 times the clinical exposure. Firsocostat was considered non-corrosive and does not require classification as an eye irritant.

Based on the systemic concentrations of firsocostat measured in the repeat-dose toxicity studies in mice, rat and dog at the projected clinically efficacious AUC (88 ng•h/mL), the margins of exposure at the NOAELs are 8, 206 and 48 in the mouse, rat and dog, respectively. Thus, data from the nonclinical studies support the continued clinical evaluation of 20 mg firsocostat.

Please refer to the firsocostat IB for additional details.

1.4.4. Nonclinical Pharmacokinetics

Firsocostat is highly protein bound in plasma, and the volume of distribution of firsocostat across nonclinical species is greater than total body water (0.7 L/kg), suggesting that firsocostat is well distributed. A significant fraction of the absorbed parent compound is extracted by the liver indicating that firsocostat is available to the target site (ie, the liver).

The metabolism of firsocostat has been evaluated in in vitro incubations of rat, dog, Cynomolgus monkey, and human hepatocytes. No metabolites unique to the human were detected. In vivo metabolite identification studies in Sprague-Dawley rat and Beagle dog have demonstrated that the primary metabolite of firsocostat is the glucuronide conjugate, NDI-011535, renamed as GS-834773.

Neither firsocostat nor GS-834773 inhibits the cytochrome P450 (CYP) enzymes involved in drug metabolism. Firsocostat is not an inducer of CYP1A2 or CYP2B6 isozymes and is a mild inducer of CYP3A4 in human hepatocytes in vitro.

A single nonclinical study to evaluate elimination of firsocostat and the metabolite GS-834773 was performed in bile duct cannulated Sprague-Dawley rats to profile concentrations over time in plasma, urine, and bile. Overall, the pharmacokinetic (PK) profile in plasma and bile indicate that firsocostat is rapidly cleared from the plasma compartment, and the primary route of elimination is via the bile.

Please refer to the firsocostat IB for additional details.

1.4.5. Clinical Trials of Firsocostat

As of 27 November 2017, 12 Phase 1 and 2 Phase 2 clinical studies have been completed or are ongoing.

Information about completed and ongoing clinical studies can be found in the firsocostat IB.

1.4.5.1. Study GS-US-426-4074: A Phase 1 Study to Evaluate Transporter and Cytochrome (CYP) 450-Mediated Drug-Drug Interactions between Firsocostat and Probe Drugs

Study GS-US-426-4074 is an ongoing, open-label, multiple-cohort study designed to evaluate transporter and CYP-mediated drug-drug interactions (DDIs) between firsocostat (10, 20, or 50 mg) and various probe drugs in healthy subjects. The effect of an organic anion-transporting polypeptide (OATP)1B1/1B3 inhibitor on the PK/PD relationships of firsocostat, as assessed by changes in fractional DNL, will also be evaluated.

1.4.5.1.1. Subject Disposition

As of 1 November 2017, a total of 90 subjects were dosed; 88 subjects had completed study treatment. Two subjects discontinued early. One subject withdrew on Study Day 23 due to personal reasons, and the second subject withdrew on Study Day 8 following a positive pregnancy test.

1.4.5.1.2. Preliminary Safety Results

Forty-eight out of 90 subjects (53.3%) experienced an AE. Of these subjects, 10 subjects experienced AE(s) that were deemed related to the study drug. The most common AE was headache (20%). All of these AEs were Grade 1 or 2, and no subject discontinued the study due to an AE.

Fourteen subjects (15.6%) experienced a Grade 3 lab abnormality. Thirteen of these subjects had asymptomatic hematuria (3+) on their urine dipstick, and all were menstruating females. One subject had a Grade 3 asymptomatic elevation of their total and low-density lipoprotein (LDL) cholesterol, and one subject had a transient Grade 3 decrease in hemoglobin. There were no Grade 4 lab abnormalities.

1.4.5.1.3. Preliminary PK Results

Preliminary PK results from the following cohorts are presented below and in Table 1-2.

Cohort 1: Impact of OATP/multidrug resistance-associated protein 2 (MRP2)/permeability glycoprotein (P-gp) inhibition (single dose cyclosporine [CsA] 600 mg: CsA) or OATP1B1/1B3 inhibition (single dose rifampin [RIF] 600 mg: RIF) on single dose of firsocostat 20 mg (N 28). Single doses of CsA and RIF significantly increased firsocostat exposure (21.2- and 18.4-fold, respectively) and resulted in even greater increases in GS-834773 exposures (64.5- and 55.4-fold, respectively). These data indicate firsocostat is a sensitive substrate of hepatic OATP with intestinal P-gp playing a minimal role in firsocostat absorption as seen by a smaller increase in firsocostat C_{max} by CsA compared to single dose RIF.

Cohort 2: Impact of pan-UGT inhibition (probenecid [PBC] 500 mg: PBC) and CYP3A4 inhibition (voriconazole [VORI] 200 mg: VORI) on single dose administration of firsocostat 20 mg (N 14). Co-administration of firsocostat with PBC resulted in a moderate increase in firsocostat exposure (61%) indicating UGTs are involved in the metabolism of firsocostat. The moderate increase in GS-834773 exposure (74%) with PBC may be due to inhibition of other enzymes/transporters involved in the clearance of GS-834773. Co-administration of firsocostat with VORI increased firsocostat and GS-834773 exposures (37% and 44%, respectively) indicating CYP3A4 plays a small role in the elimination of both parent and metabolite.

Cohort 5: Impact of single and multiple doses of firsocostat 50 mg once daily on a sensitive CYP3A4 probe substrate (midazolam [MDZ] 2 mg: MDZ; N 12). Neither single dose nor multiple doses of firsocostat altered MDZ exposure (90% CIs of the % geometric mean ration (GMR) for AUC and C_{max} with lack of effect bounds of 70-143%) indicating firsocostat is not an inhibitor or inducer of CYP3A4.

Cohort 6: Impact of single and multiple doses of firsocostat 50 mg once daily on a representative combined oral contraceptive (drospirenone [DRSP]/EE 3/0.02 mg: DRSP/EE; N 16). There was no effect of single dose firsocostat on DRSP or EE exposure (90% CIs of the %GMR for AUC and C_{max} with lack of effect bounds of 70-143%). Multiple doses of firsocostat slightly increased EE exposure (AUC_{inf} increased ~34%) with no effect on DRSP exposure indicating firsocostat does not induce enzymes/transporters involved in the clearance of DRSP or EE. No loss of contraceptive efficacy is expected upon administration of firsocostat with oral contraceptives like DRSP/EE. The slight increase in EE exposure is not considered clinically significant and does not warrant dose modification.

Table 1-2. Preliminary Pharmacokinetic Results from Study GS-US-426-4074 Evaluating DDIs with Firsocostat (20 mg or 50 mg)

Inhibitor/Inducer Drug	Firsocostat %GMR (90% CIs)		GS-834773 %GMR (90% CIs)	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
CsA	2120 (1810, 2480)	2000 (1590, 2520)	6450 (5260, 7900)	7870 (6130, 10100)
RIF	1840 (1570, 2150)	2710 (2160, 3400)	5540 (4520, 6790)	10100 (7890, 13000)
PBC	161 (144, 180)	160 (132, 195)	174 (148, 204)	176 (145, 214)
VORI	137 (123, 152)	145 (119, 176)	144 (123, 170)	140 (116, 171)
	MDZ + SD Firsocostat %GMR (90% CIs)		**MDZ + MD Firsocostat %GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
Firsocostat (50 mg)	111 (99.8, 123)	102 (91.6, 115)	102 (91.4, 113)	106 (94.9, 119)
	DRSP + SD Firsocostat **%GMR (90% CIs)**		**DRSP + MD** Firsocostat **%GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
Firsocostat (50 mg)	96.4 (86.5, 107)	103 (91.5, 116)	105 (94.0, 117)	116 (102, 131)
	EE + SD Firsocostat **%GMR (90% CIs)**		**EE + MD** Firsocostat **%GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
Firsocostat (50 mg)	102 (87.6, 119)	112 (104, 122)	134 (114, 156)	121 (111, 131)

SD single dose
MD multiple dose
Data reported to 3 significant figures

1.4.6. Study GS-US-426-3988: A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of Firsocostat or Fenofibrate in Subjects with Normal and Impaired Hepatic Function

Study GS-US-426-3988 is an ongoing Phase 1, open-label, parallel-group, single dose study evaluating the safety, tolerability, and PK of firsocostat or fenofibrate in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment (CP class A, B, or C, respectively). Up to 80 subjects are planned for Enrollment in 1 of 4 hepatic impairment cohorts: Cohort 1 (mild hepatic impairment), Cohort 2 (moderate hepatic impairment), Cohort 3 (severe hepatic impairment), and Cohort 4 (mild hepatic impairment). Within each cohort, each subject with impaired hepatic function (N 10 per cohort) will be matched for age (± 10 years),

sex, race, and body mass index (BMI): ± 15% with a control subject with normal hepatic function (N 10 per cohort). Data from healthy subjects may be used in >1 cohort if a subject was an appropriate match for a subject with hepatic function in >1 cohort. Subjects in Cohorts 1 and 2 will receive a single oral dose of firsocostat 20 mg in a fasted state on Day 1. Subjects in Cohort 3 will receive a single oral dose of firsocostat5 mg in a fasted state on Day 1. Subjects in Cohort 4 will receive a single oral dose of fenofibrate 48 mg in a fasted state on Day 1.

1.4.6.1. Subject Disposition and Demographics

As of 19 April 2019 a total of 72 subjects were dosed; 67 subjects had completed study treatment. No subjects prematurely discontinued study treatment. No subjects withdrew consent, and no subjects were lost to follow-up.

1.4.6.2. Preliminary Safety Results

In the mild hepatic impairment cohort, 1 subject (10%) had a treatment-related AE of facial flushing that was Grade 1. One other mild hepatic impairment subject had a Grade 1 headache. Two healthy matched controls experienced Grade 1 AEs of headache and herpes simplex virus type 2. In the moderate hepatic impairment cohort, 1 subject had a Grade 1 headache that was deemed not-related to study drug. There was no Grade 3 or 4 AEs in either cohort. No AEs led to dose modification, interruption, or premature discontinuation of study drug. There were no SAEs, pregnancies, or deaths.

In the mild hepatic impairment cohort, 4 subjects had Grade 3 lab abnormalities. Elevations in GGT (2 subjects) and LDL cholesterol (2 subjects) were the most common, and all Grade 3 lab abnormalities of GGT and LDL were present at Screening. In the healthy matched controls, 2 subjects also had Grade 3 LDL cholesterol lab abnormalities that were present at Day 1. In the moderate hepatic impairment cohort, 3 subjects had Grade 3 lab abnormalities (decreased lymphocytes, hypomagnesemia, and hyponatremia). There were no Grade 4 lab abnormalities.

1.4.6.2.1. Preliminary PK Results

Preliminary PK results from Cohorts 1 and 2 are presented below and in:

- Cohort 1 (Mild Hepatic Impairment; CP A): firsocostat exposure (AUC_{inf} and C_{max}) was higher in subjects with mild hepatic impairment (approximately 84% and 69%, respectively) as compared to subjects with normal hepatic function. In subjects with mild hepatic impairment, exposure (AUC_{inf} and C_{max}) of the metabolite GS-834773 was also higher (approximately 3.9-fold higher for both). Plasma protein binding of both parent and metabolite were similar in subjects with mild hepatic impairment as compared to subjects with normal hepatic function. firsocostat is a hepatic OATP substrate and OATP expression/activity may be reduced in patients with cirrhosis. Thus, altered OATP expression/activity may contribute to the observed higher systemic exposure of firsocostat. At a dose of 20 mg once daily (QD) in subjects with mild hepatic impairment, exposure margins relative to preclinical NOAEL exposures for both parent and metabolite are expected to remain adequate.

- Cohort 2 (Moderate Hepatic Impairment; CP B): firsocostat exposure (AUC_{inf} and C_{max}) was higher in subjects with moderate hepatic impairment (approximately 8.7- and 9.1-fold higher, respectively) as compared to subjects with normal hepatic function. Exposure (AUC_{inf} and C_{max}) of the metabolite GS-834773 was also higher (approximately 37.5- and 44.7-fold higher, respectively). Plasma protein binding of both parent and metabolite were similar in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function. The increased exposure of firsocostat and GS-834773 in subjects with moderate hepatic impairment is likely due to further decreases in OATP expression/activity relative to mild hepatic impairment as well as decreases in expression/activity of enzymes involved in firsocostat metabolism (ie, UGTs and CYP3A4). At a dose of 20 mg QD, firsocostat plasma exposures in subjects with moderate hepatic impairment are ≥ 5-fold and ≥ 25-fold lower than exposures at the NOAEL in the chronic toxicology studies in dogs and rats, respectively.

Table 1-3. GS-US-426-3988: Preliminary Firsocostat and GS-834773 PK Parameters Following a Single Dose of Firsocostat 20 mg in Subjects with Mild or Moderate Hepatic Impairment or Normal Hepatic Function

Cohort	Analyte	Mean (%CV) PK Parameter	Matched Healthy Control (N=10)	Moderate Hepatic Impairment (N=10)	%GMR (90% CI)
1 (Mild HI)	Firsocostat	AUC_{inf} (hr.ng/mL)	70.4 (55.2)	166 (98.2)	184 (101, 336)
		AUC_{last} (hr.ng/mL)	69.6 (55.7)	161 (98.5)	181 (99.3, 331)
		C_{max} (ng/mL)	25.4 (80.6)	50.9 (90.3)	169 (87.5, 325)
	GS 834773	AUC_{inf} (hr.ng/mL)	8.29 (69.6)	48.1 (123)	387 (177, 846)
		AUC_{last} (hr.ng/mL)	7.38 (79.0)	46.3 (125)	430 (187, 990)
		C_{max} (ng/mL)	2.29 (91.8)	12.9 (125)	391 (164, 935)
2 (Moderate HI)	Firsocostat	AUC_{inf} (hr.ng/mL)	65.9 (52.3)	687 (72.8)	867 (484, 1550)
		AUC_{last} (hr.ng/mL)	64.5 (51.5)	681 (72.9)	879 (491, 1580)
		C_{max} (ng/mL)	20.1 (60.2)	198 (60.0)	905 (539, 1520)
	GS 834773	AUC_{inf} (hr.ng/mL)	5.9 (57.5)	399 (135)	3750 (1640, 8560)
		AUC_{last} (hr.ng/mL)	5.1 (62.9)	396 (136)	4410 (1900, 10200)
		C_{max} (ng/mL)	1.4 (81.2)	77.3 (72.5)	4470 (2190, 9130)

Data presented to 3 significant figures

Based on the preliminary PK data from this study as well as the overall safety profile of firsocostat, dose adjustments are not considered necessary in subjects with mild hepatic impairment.

1.4.6.3. A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Firsocostat in Subjects with Nonalcoholic Steatohepatitis (GS-US-426-3989)

Please refer to the firsocostat IB for additional details.

1.5. Rationale for This Study

NASH involves a complex interplay between hepatocytes, immune cells, and hepatic stellate cells that perpetuates a pathological cycle of hepatocyte injury, inflammation and fibrosis {Caligiuri 2016}. Increased synthesis and accumulation of fatty acids in hepatocytes leads to lipotoxicity, a state characterized by increased production of toxic lipid metabolites, bile acids, ROS, growth factors, and ultimately hepatocyte cell death {Neuschwander-Tetri 2010}. These metabolic stress signals directly promote the activation and differentiation of hepatic stellate cells into myofibroblasts, the primary source of collagen and extracellular matrix that causes fibrosis. In addition, hepatocyte lipotoxicity promotes an immune response by resident macrophages, which produce ROS, growth factors and cytokines such as transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF), that further increase myofibroblast activation, migration, proliferation and survival, and result in fibrosis {Lee 2015}. Based on the multiple biological pathways involved in the pathogenesis of NASH, and the heterogeneity of the patient population, it is likely that a combination of drugs that have distinct mechanisms of action will be required to achieve optimal therapeutic benefit.

Both human and animal studies have shown a beneficial effect of GLP-1 RA on liver lipid metabolism, inflammation, and progression of fatty liver to NASH {Gao 2015, Lee 2012, Mells 2012, Panjwani 2013}. The investigator sponsored study **L**iraglutide **E**fficacy and **A**ction in **N**ASH (LEAN), enrolled 52 overweight subjects with and without T2D, with biopsy-confirmed NASH to receive liraglutide s.c. or placebo once daily. After 48 weeks of treatment, 9 out of 23 (39%) subjects treated with liraglutide had resolution of NASH with no worsening of fibrosis (relative risk 4.3 [1.0 17.7] 95% CI; p 0.019) compared to 2 out of 22 (9%) subjects treated with placebo. Furthermore, significantly fewer patients treated with liraglutide had worsening of fibrosis compared to placebo {Armstrong 2016}. As semaglutide is structurally similar to liraglutide with similar mechanism of action and with potential for more pronounced effect on glycemic control and body weight, semaglutide is thought to be a potential candidate for treatment of NASH, both alone and in combination with other agents.

As previously noted, increased rates of hepatic DNL and insufficient fatty acid oxidation lead to hepatic steatosis and associated lipotoxicity, which are implicated in the etiology and progression of NASH. By inhibiting ACC, firsocostat has been shown to reduce steatosis and fibrosis in animal models of NASH and to reduce DNL by >70% at doses of 20 mg daily in humans. In a recently-completed Phase 2 study in subjects with NASH (GS-US-426-3989), firsocostat led to improvement in hepatic steatosis, liver biochemistry, and markers of fibrosis.

FXR agonism has been shown to reduce hepatic lipid and bile acid synthesis due to down regulation of sterol regulatory element binding protein-1c (SREBP-1c) and cytochrome P450 7A1 (CYP7A1), respectively, as well as reduce insulin resistance and hepatic gluconeogenesis {Zhang 2006}. Animal models have demonstrated the ability of cilofexor to reduce hepatic fibrosis in a choline-deficient high fat diet/$NaNO_2$ rat model of NASH and to reduce hepatic steatosis in obese mice fed a fat and carbohydrate rich diet. In the proof of concept study (GS-US-384-3914), cilofexor led to statistically significant reductions in hepatic steatosis and GGT, and thus, cilofexor is postulated to have these and other benefits with longer duration of dosing.

Preclinical studies in animal models of NASH have demonstrated that combinations of an FXR agonist and ACC inhibitor lead to greater efficacy to reduce hepatic steatosis and measures of liver fibrosis compared to the respective monotherapies. Combination toxicology studies have revealed no new toxicities of the combination of cilofexor and firsocostat.

In the proof of concept combination study (GS-US-384-3914), 20 subjects received firsocostat 20 mg and cilofexor 30 mg once daily for 12 weeks. 73.7% of subjects (14 of 19 evaluable subjects) had at least a 30% relative reduction in MRI-PDFF. The subjects on this regimen also had significant median relative reductions in liver biochemistry (i.e., ALT, GGT) and FibroSure®/FibroTest® after 12 weeks of treatment. From a safety perspective, these subjects had similar rates of AEs compared to monotherapy treatment with firsocostat or cilofexor treatment alone for 12 weeks in this study.

In previous and ongoing studies with firsocostat and cilofexor (GS-US-426-3989, GS-US-402-1852, GS-US-384-3914, and GS-US-454-4378), subjects have been concurrently treated with GLP-1 agonists including liraglutide and semaglutide for diabetes. Because these were well tolerated previously, there is no indication of an increased safety concern with the combinations for this study.

Given the complex pathophysiology of NASH and the belief that combination regimens are likely to be the most efficacious, as well as the hypothesis that weight loss is a key driver of NASH resolution in patients without advanced fibrosis, supported by earlier clinical studies with liraglutide, this study aims to evaluate the safety and tolerability of combining semaglutide (an agent approved for treatment of type 2 diabetes, and in clinical testing for weight loss treatment and NASH) with cilofexor and firsocostat which address separate but complementary pathophysiologic pathways in this complex disease.

1.5.1. Rationale for Dose Selection of Semaglutide

The proposed target dose of semaglutide 2.4 mg once weekly in the Phase 3 weight management study (NN9536) 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 subjects with obesity showed that the semaglutide 0.4 mg once-daily dose was the greatest effecton weight loss while displaying an acceptable tolerability profile. Furthermore, data from the semaglutide s.c. T2D development program (SUSTAIN trials with once-weekly dosing and study NN9535-4191 with once-daily s.c. dosing of up to 0.3 mg/day) did not support the hypothesis that once-daily dosing provides better gastrointestinal (GI)tolerability as compared to

once-weekly dosing. Hence, the proportion of subjects with GI AEs and the rates of such events were generally higher in study NN9535-4191 and in study NN9536-4153 where semaglutide was dosed once daily as compared to the Phase 3a trials where semaglutide was dosed once weekly.

Based on population pharmacokinetic modelling, it was estimated that the C_{max} at steady-state, with a once-weekly maintenance dose of 2.4 mg semaglutide s.c., will not exceed that obtained with the once-daily 0.4 mg semaglutide s.c. dose investigated in study NN9536-4153. When comparing the simulated human exposure at 2.4 mg/week to the animal exposures at the NOAEL, exposure ratios are above 1, indicating that exposure at 2.4 mg is supported by the nonclinical studies. Consequently, the proposed semaglutide s.c. target dose for the Phase 3 weight management development program is 2.4 mg once weekly.

It is well known that to mitigate GI side effects with GLP-1 RA treatment, dose escalation to the target dose is required. Based on experience from the semaglutide s.c. T2D development program and study NN9536-4153, 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.

1.5.2. Rationale for the Dose Selection of Cilofexor

This study will evaluate the safety and tolerability of 30mg and 100mg cilofexor QD in combination with semaglutide over 24 weeks in subjects with NASH. These doses were selected based on short-term safety, PK and PD results from Study GS-US-402-1851 in healthy subjects.

In the Phase 1 study GS-US-402-1851, cilofexor was tested at doses ranging from 10 to 300 mg once daily for up to 14 days and was well tolerated. Across the range of cilofexor doses evaluated, doses ≥ 30 mg provided comparable intestinal FXR agonism as assessed by increases in FGF19 exposure. Food, by slowing oral absorption of cilofexor, resulted in prolonged elevation of plasma FGF19 concentrations. Exposure-response relationships showed that changes in C4 exposure are negatively correlated with changes in exposure of FGF19 and cilofexor.

In a Phase 2 study GS-US-402-1852, evaluating the safety, tolerability and efficacy of 30 mg and 100 mg cilofexor in subjects, 140 NASH patients were treated with cilofexor 100 mg, cilofexor 30 mg or placebo orally once daily for 24 weeks. A decline of at least 30% in hepatic fat measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) was observed in 38.9% of patients treated with cilofexor 100 mg (p 0.011 vs placebo), 14% treated with cilofexor 30 mg (p 0.87), and 12.5% with placebo. Improvements in liver biochemistry tests (serum GGT) and markers of reduced bile acid synthesis (serum C4 and bile acids) were observed in the 30 mg and 100 mg arms of cilofexor -treated patients. Cilofexor was generally well tolerated; moderate to severe pruritus, or itching, occurred in 14% of patients in the cilofexor 100 mg arm compared to 4% in the cilofexor 30 mg and placebo arms. Changes in lipid profile and glycemic parameters did not differ between cilofexor and placebo-treated patients. The most common adverse events in patients treated with cilofexor were pruritus, upper respiratory tract infection, headache and fatigue. Treatment was discontinued due to adverse events in one patient treated with cilofexor 100 mg (2%), five patients treated with cilofexor 30 mg (9%), and two patients with placebo (7%).

1.5.3. Rationale for the Dose Selection of Firsocostat

The dose of firsocostat chosen for evaluation in this study, 20 mg QD, is supported by the safety, tolerability and effects of firsocostat on DNL from studies 0976-101, 0976-102, and 0976-103 described in the IB, the efficacy observed in the Phase 2 NASH study (GS-US-426-3989), and the safety of firsocostat in subjects with cirrhosis due to NASH (proof of concept study GS-US-384-3914), including those with mild hepatic impairment (GS-US-426-3988). In healthy subjects, single doses of firsocostat up to 1000 mg or multiple daily doses (10 days) of firsocostat up to 200 mg were administered. In healthy but overweight or obese subjects, a single firsocostat dose of 20 mg resulted in a mean inhibition of fractional DNL of 71%. In study GS-US-426-3989, firsocostat 5 mg and 20 mg were evaluated for 12 weeks in subjects 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 MRI-PDFF. firsocostat 20 mg also had larger reductions in liver biochemistry (i.e., ALT) and serum markers of fibrosis (i.e., tissue inhibitor of metalloproteinase 1 (TIMP-1) and procollagen III amino terminal peptide (PIIINP)). In study GS-US-426-3989, approximately 40% of subjects were presumed to have advanced fibrosis at baseline based on MRE values ≥ 3.64 kPa and/or ELF™ Test scores ≥ 9.8. These subjects showed similar efficacy and safety profiles as subjects with less advanced fibrosis according to these noninvasive markers of fibrosis. Also, subjects with cirrhosis due to NASH have been dosed with firsocostat 20 mg for 12 weeks in the proof of concept study described above with similar safety as subjects with less advanced fibrosis.

Additionally, nonclinical toxicology studies up to 26 and 39 weeks in duration have been conducted in rats and dogs, respectively, at exposure margins multiple folds above the expected clinical exposure. Firsocostat exposures in non-cirrhotic subjects are expected to remain > 48-and 206-fold lower than the firsocostat exposures observed at the NOAELs in the 39-week dog and 26-week rat toxicity studies, respectively. Based on preliminary data from Study GS-US-426-3988, firsocostat exposures in subjects with mild hepatic impairment (CP A) are expected to remain ≥ 22 and ≥105-fold lower than the firsocostat exposures observed at the NOAELs in the 39-week dog and 26-week rat toxicity studies, respectively. Based on preliminary PK data in subjects with mild hepatic impairment and the overall safety profile of firsocostat, dose adjustments are not considered necessary for subjects with compensated cirrhosis in this study.

1.5.4. Rationale for Study Population

The progression from NAFLD to NASH to cirrhosis occurs over decades. The highest levels of morbidity and mortality are found in NASH patients with advanced fibrosis and cirrhosis {Ekstedt 2014, Yeh 2014}. Thus, evaluating agents in this patient population is anticipated to have the greatest impact on morbidity and mortality.

Inclusion criteria for this study were developed in order to enrich this small proof-of-concept study with subjects who have definite inflammatory and fibrotic processes that can be measured both through a historical biopsy and non-invasive tests. Specifically, all subjects must either have histologic evidence of NASH with F2-3 fibrosis, or have a clinical diagnosis of NAFLD with evidence of ≥ 10% hepatic steatosis on MRI-PDFF {Bannas 2015}, a Screening FibroTest® <0.75 (unless historical liver biopsy does not reveal cirrhosis), and a FibroScan® with liver stiffness >7 kPa.

Based on these criteria, subjects enrolled without a historical liver biopsy will have a high probability of NASH with fibrosis, a population with a large unmet medical need {Loomba 2014}.

Ongoing clinical trials are evaluating the efficacy of cilofexor and firsocostat in combination for subjects with NASH with bridging fibrosis and compensated cirrhosis. Given the potential benefits of semaglutide in the NASH patient population, this study will evaluate the safety and tolerability of a GLP-1 receptor agonist as a component of future combination therapy for NASH (i.e., in addition to cilofexor or firsocostat alone, or to both).

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of study drug(s) in subjects with NASH.

CCI

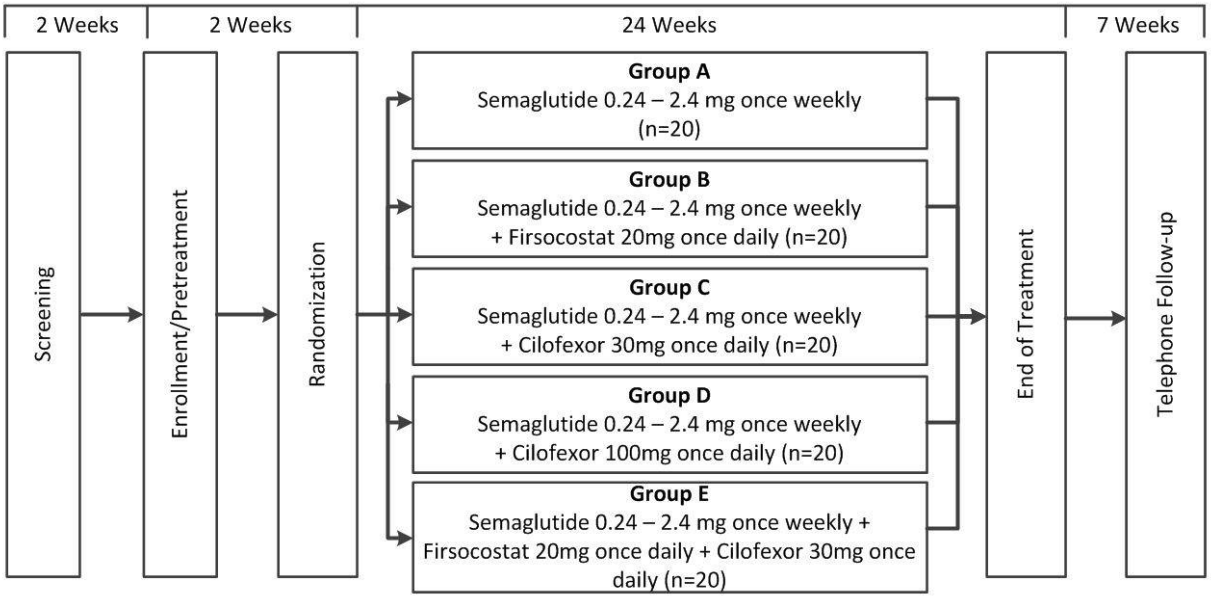
3. STUDY DESIGN

3.1. Study Design

This is a proof of concept, open-label study evaluating the safety, tolerability, and efficacy of monotherapy and combination regimens in subjects with NASH.

Subjects meeting the study's entry criteria will be randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 treatment groups, with approximately 20 subjects in each group, as shown in the figure below:

Figure 3-1. Overall Study Design



Randomization will be stratified by the presence or absence of type 2 diabetes mellitus, as determined by medical history or based on the Screening laboratory values if previously undiagnosed (hemoglobin A1c [HbA1c] ≥ 6.5%).

3.2. Study Treatments

Subjects meeting the study's entry criteria will be randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 treatment groups, with approximately 20 subjects in each group, as shown in the Figure 3-1.

3.3. Duration of Study

Participation in the study can last up to 35 weeks, which includes a 2-week Screening period, a 2 week Pre-Treatment period, up to a 24-week Treatment period, and a 7-week Follow-Up period.

3.4. End of Study

End of study is considered to be completion of the Telephone Follow-Up visit.

3.5. Post Study Care

There is no offered post study care.

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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will enroll approximately 100 subjects with a clinical diagnosis of nonalcoholic fatty liver disease (NAFLD) with a Screening FibroTest® < 0.75 (unless all historical liver biopsies do not reveal cirrhosis), a Screening MRI-PDFF with ≥ 10% steatosis (as assessed by the central reader), and a Screening FibroScan® with liver stiffness ≥ 7 kPa, OR subjects with a historical liver biopsy within 6 months of the date of the Screening Visit consistent with NASH (defined as the presence of steatosis, inflammation, and ballooning) with stage 2-3 fibrosis according to the NASH Clinical Research Network (CRN) classification (or equivalent).

4.2. Inclusion Criteria

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

1) Males and females between 18-75 years of age inclusive, based on the date of the Screening Visit;

2) Willing and able to provide informed consent prior to any study specific procedures being performed;

3) Subjects must meet all of the following conditions (a-d) OR (e):

   a. Clinical diagnosis of nonalcoholic fatty liver disease (NAFLD);

   b. Screening FibroTest® < 0.75, unless all previous historical liver biopsies do not reveal cirrhosis. In subjects with Gilbert's syndrome or hemolysis, FibroTest® will be calculated using direct bilirubin instead of total bilirubin;

   c. Screening MRI-PDFF with ≥ 10% steatosis, as assessed by the central reader. Historical MRI-PDFF within 4 weeks of the date of the Screening Visit may be used if deemed acceptable by the central reader;

   d. Screening FibroScan® with liver stiffness ≥ 7 kPa. Historical FibroScan® within 4 weeks of the date of the Screening Visit is acceptable;

   OR

   e. An historical liver biopsy within 6 months of the date of the Screening Visit consistent with NASH (defined as the presence of steatosis, inflammation, and ballooning) with stage 2-3 fibrosis according to the NASH Clinical Research Network (CRN) classification (or equivalent). Report will be reviewed by the Medical Monitor;

4) Subject has the following laboratory parameters at the Screening Visit, as determined by the central laboratory:

   a. Alanine aminotransferase (ALT) ≤ 5 x ULN;

   b. eGFR ≥ 30 milliliter/minute (mL/min), as calculated by the MDRD study equation;

   c. HbA1c ≤ 9.5% (or serum fructosamine ≤ 381 μmol if HbA1c is unable to be resulted);

   d. INR ≤ 1.2, unless due to therapeutic anti-coagulation therapy;

   e. Platelet count ≥ 100,000/μL;

   f. Total bilirubin < 1.3 x ULN unless alternate etiology such as Gilbert's syndrome present;

   g. Calcitonin ≤ 100 ng/L;

5) Body Mass Index (BMI) > 23 kg/m^2 and body weight of > 60 kg;

6) A negative serum pregnancy test is required for female subjects of childbearing potential as defined in Appendix 3;

7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Documented weight loss > 5% within 6 months of the date of the Screening Visit;

2) Any historical liver biopsy consistent with cirrhosis;

3) Pregnant or lactating females;

4) Alcohol consumption greater than 21 oz/week for males or 14 oz/week for females (1oz/30 mL of alcohol is present in 1 12oz/360 mL beer, 1 4oz/120 mL glass of wine, and a 1oz/30 mL measure of 40% proof alcohol);

5) Positive urine screen for amphetamines, cocaine or opiates (ie, heroin, morphine) at Screening. Subjects on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to the date of Screening Visit may be included in the study. Subjects with a positive urine drug screen due to prescription opioid-based or amphetamine-based medication are eligible if the prescription and diagnosis are reviewed and approved by the investigator;

6) Any history of decompensated liver disease, including ascites, hepatic encephalopathy, or variceal bleeding;

7) Other causes of liver disease, including but not limited to: alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders (eg, primary biliary cholangitis [PBC], primary sclerosing cholangitis [PSC], autoimmune hepatitis), drug-induced hepatotoxicity, Wilson disease, clinically significant iron overload, or alpha-1-antitryspin deficiency requiring treatment;

8) History of liver transplantation;

9) History of hepatocellular carcinoma;

10) Weight reduction surgery in the past 2 years or planned during the study;

11) Chronic hepatitis B (HBsAg positive);

12) Chronic hepatitis C (HCV RNA positive). Subjects cured of HCV infection less than 2 years prior to the date of the Screening Visit are not eligible;

13) HIV Ab positive;

14) Unstable cardiovascular disease as defined by any of the following:

    a. Unstable angina, myocardial infarction, coronary artery bypass graft surgery or coronary angioplasty within 6 months prior to the date of the Screening Visit;

    b. Transient ischemic attack or cerebrovascular accident within 6 months prior to the date of the Screening Visit;

    c. Symptomatic obstructive valvular heart disease or hypertrophic cardiomyopathy;

    d. Symptomatic congestive heart failure;

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

    f. An emergency room visit or hospitalization for confirmed cardiovascular disease within 6 months prior to the date of the Screening Visit;

15) History of a malignancy within 5 years of the date of the Screening Visit with the following exceptions:

    a. Adequately treated carcinoma in situ of the cervix;

    b. Adequately treated basal or squamous cell cancer or other localized non-melanoma skin cancer;

16) Presence of acute pancreatitis within the past 180 days prior to the date of the Screening Visit;

17) History or presence of chronic pancreatitis;

18) Presence or history of type 1 diabetes mellitus;

19) For subjects with type 2 diabetes diagnosed prior to the date of the Screening Visit OR on Screening Visit labs (defined as HbA1c ≥6.5%), subjects must have no evidence of uncontrolled and potentially unstable retinopathy or maculopathy as determined by:

    a. A fundus exam performed in the 90 days prior to the date of the Screening Visit. If there has been worsening of the subject's visual function since this historical fundus exam in the opinion of the investigator, then the fundus exam must be repeated;

    OR

    b. A fundus exam performed between the date of the Screening Visit and Enrollment (Day -14)

    Pharmacological pupil-dilation is a requirement in both of the above cases unless using a digital fundus photography camera specified for non-dilated examination;

20) Personal or first degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma;

21) Treatment with GLP-1 RAs in the period from 90 days prior to the date of the Screening Visit;

22) Subjects on Vitamin E regimen ≥800 IU/day must be on a stable dose (defined as no changes in prescribed dose, new Vitamin E containing medications, or discontinuation) for at least 180 days prior to the date of the Screening Visit and in the period between the date of the Screening Visit and Enrollment (Day -14);

23) Subjects on antidiabetic medications must be on a stable dose for at least 90 days prior to the date of the Screening Visit and in the period between the date of the Screening Visit and Enrollment (Day -14);

24) Use of any prohibited concomitant medications as described in Section 5.6;

25) Any investigational medication or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to the date of the Screening Visit throughout the study (e.g., obeticholic acid, elafibranor, and cenicriviroc) is prohibited;

26) Known hypersensitivity to the study drug, the metabolites, or formulation excipient.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization

An Interactive Web Response System (IWRS) will be used for centralized randomization and treatment assignment. Randomization will be stratified by the presence or absence of type 2 diabetes mellitus, as determined by medical history or based on the Screening Visit lab values if previously undiagnosed (HbA1c $\geq$ 6.5%).

Investigative site personnel will obtain the subject's identification number and study drug assignment from the IWRS. Study drugs will be dispensed by the study pharmacist, or designee to the subjects.

Study drugs will be dispensed in an open-label fashion to the subjects.

5.2. Description and Handling of Semaglutide 3.0 mg/mL

The drug product formulation for the semaglutide solution for injection has the composition shown in Table 5-1. All other ingredients 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 5-1. Composition of Semaglutide Solution for Injection

Name of ingredient	Function	Pharmacopoeia
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

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

5.2.1. PDS290 pen-injector for Semaglutide for use in Clinical Trials

Device Information

The PDS290 pen-injector for semaglutide is a dial-a-dose prefilled device integrated with a 3 mL cartridge filled with semaglutide 3.0 mg/mL. 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 semaglutide can be used multiple times until either the in-use time has passed or the cartridge is empty. 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 semaglutide are included in the directions for use (DFU) provided to trial sites and to be provided directly to subjects. Storage instructions are printed on the drug product label and are also provided in the Site Operations Manual. Investigators must ensure that these instructions are strictly followed.

Regulatory Status

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

Existing Clinical Data

The adequate safety and performance of the PDS290 pen-injector for semaglutide (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 post-market safety data for the PDS290 pen-injector family. It is concluded that the PDS290 pen-injector for semaglutide (3.0 mg/mL) gives a favorable benefit-risk profile for administration of semaglutide in NASH clinical trials.

Thus far, no clinical trials have been completed with the PDS290 pen-injector for semaglutide (3.0 mg/mL) in NASH clinical programs.

5.2.2. Storage and Handling

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

5.2.3. Shelf-life and in-use time for Semaglutide in PDS290

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

5.3. Description and Handling of Cilofexor (GS-9674)

5.3.1. Formulation

Cilofexor is supplied as 100 mg and 30 mg strength (as free form equivalent) tablets. The tablets contain cilofexor-02 (tromethamine salt) and the following inactive ingredients: mannitol, microcrystalline cellulose, crospovidone, magnesium stearate and film-coating material polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, yellow iron oxide and black iron oxide. Cilofexor 100 mg tablets are capsule-shaped, film-coated green tablets debossed with “100” on one side and “GSI” on the other side. Cilofexor 30 mg tablets are round, film-coated green tablets debossed with “30” on one side and “GSI” on the other side.

5.3.2. Packaging and Labeling

Cilofexor 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, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA) and/or other local regulations.

5.3.3. Storage and Handling

Study drug cilofexor should be stored below 30°C (86 °F). Storage conditions are specified on the label.

Until dispensed to the subjects, all bottles of study drugs 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. 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 cilofexor tablets.

5.4. Description and Handling of Firsocostat (GS-0976)

5.4.1. Formulation

Firsocostat tablets are round, plain-faced, film-coated white tablets containing 20 mg firsocostat. In addition to the active ingredient, firsocostat tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

5.4.2. Packaging and Labeling

Firsocostat tablets are packaged in white HDPE bottles. Each bottle contains 30 tablets 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 centers in the US shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA) and/or other local regulations.

5.4.3. Storage and Handling

Firsocostat tablets should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label.

Until dispensed to the subjects, all bottles of study drugs 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. 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.

5.5. Dosage and Administration

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

Firsocostat and cilofexor tablets will be provided by Gilead Sciences, Inc. and semaglutide 3.0 mg/ml in PDS290 pen-injectors will be provided by Gilead Sciences, Inc. and manufactured by Novo Nordisk, Inc. Subjects will take semaglutide subcutaneously with a PDS290 pen-injector at approximately the same time each week. Subjects should be instructed to inject semaglutide once-weekly at the same day of the week throughout the trial. Injections may be administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. Subjects should be encouraged to inject in the same area throughout the trial, but changing between left and right side is allowed. Subjects will take firsocostat and/or cilofexor tablets (if applicable) at approximately the same time each day, with or without food, swallowed whole with water. For firsocostat and cilofexor, a dose will be considered missed if the subject cannot take the complete dose within 12 hours of their regular dosing time. If a subject misses a dose, the subject should take their next dose at the regular dosing time.

For semaglutide, if a single dose of trial product is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 48 hours. If a dose is missed and the next scheduled dose is less than 48 hours away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week. If ≥ 2 consecutive doses of trial product are missed, the subject should be encouraged to recommence the treatment if considered safe as per the investigator's discretion and if the subject does not meet any of the discontinuation criteria. The trial product should be continued as early as the situation allows. The missed doses should not affect the scheduled dosing day of the week. The start dose for re-initiation of trial product is at the investigator's discretion. In case of questions related to re-initiation of trial product, the investigator should consult the Medical Monitor.

Study drug dosing and administration will occur as follows, based on-treatment group randomization:

- Treatment Group A: Semaglutide administered subcutaneously with pre-filled pen-injector once weekly

- Treatment Group B: Semaglutide administered subcutaneously with pre-filled pen-injector once weekly, one firsocostat 20 mg tablet, administered orally once daily without regard to food

- Treatment Group C: Semaglutide administered subcutaneously with pre-filled pen-injector once weekly, one cilofexor 30 mg tablet, administered orally once daily without regard to food

- Treatment Group D: Semaglutide administered subcutaneously with pre-filled pen-injector once weekly, one cilofexor 100 mg tablet, administered orally once daily without regard to food

- Treatment Group E: Semaglutide administered subcutaneously with pre-filled pen-injector once weekly, one firsocostat 20 mg tablet administered orally once daily and one cilofexor 30 mg tablet administered orally once daily, both without regard to food

5.5.1. Management of Semaglutide Dose Escalation

After randomization semaglutide will be initiated with a starting value of 8 (0.24 mg), as shown on the dose counter of the pre-filled pen-injector, for the first 4 weeks, and subsequently the value will be increased every 4 weeks. All subjects must aim at reaching the recommended target dose of semaglutide s.c. 2.4 mg once-weekly.

Table 5-2. Semaglutide Dose Escalation Schedule

Product	Dose	Volume	Value shown in the dose counter	Duration
Semaglutide 3.0 mg/mL PDS290	0.24 mg	80 µl	8	Day 1* through Week 4
Semaglutide 3.0 mg/mL PDS290	0.50 mg	170 µl	17	Weeks 5 through 8
Semaglutide 3.0 mg/mL PDS290	1.0 mg	340 µl	34	Weeks 9 through 12
Semaglutide 3.0 mg/mL PDS290	1.7 mg	570 µl	57	Weeks 13 through 16
Semaglutide 3.0 mg/mL PDS290	2.4 mg	800 µl	80	Weeks 17 through 24

* Subject will take first dose of study drugs on site at Day 1.

If a subject does not tolerate the planned 4-week dose-escalation regimen due to GI AEs or for other reasons as judged by the investigator, the subject is allowed to stay longer at the individual dose steps. It is recommended that the Investigator aim for maximum 1 extra week on each dose level. If the planned dose escalation regimen is not adhered to, the Investigator should evaluate weekly if the dose can be escalated to the next planned level.

If a subject does not tolerate the recommended target dose of s.c. 2.4 mg once-weekly, the subject may stay at the lower dose level. This is only allowed if the subject would otherwise discontinue trial product completely and if considered safe to continue on trial product, as per the investigator's discretion. It is recommended that the subject makes at least one attempt to escalate to the recommended target dose of s.c. 2.4 mg once-weekly, as per the investigator's discretion.

It is recommended that the investigator contact the Medical Monitor 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 concomitant medications taken within 30 days prior to the date of the Screening Visit and any taken during the study until the end of the Follow-Up period.

Subjects on Vitamin E regimen ≥ 800 IU/day must be on a stable dose (defined as no changes in prescribed dose, new Vitamin E containing medications, or discontinuation) for at least 180 days prior to the date of the Screening Visit and in the period between the date of the Screening Visit and Enrollment (Day -14). If possible, the doses of these medications should remain stable through the end of study.

Subjects treated with insulin at the date of the Screening Visit:

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

Subjects treated with insulin and HbA1c ≤ 8.0 % at the date of the Screening Visit:

> Subjects treated with semaglutide 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 trial should be considered at the discretion of the investigator.

Subjects treated with sulfonylureas at the date of the Screening Visit:

> Subjects treated with semaglutide 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 trial should be considered.

Treatment with GLP-1 RAs, other than semaglutide, is prohibited in the period from 90 days prior to the date of the Screening Visit and through the end of study.

Any investigational medication or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Screening up to and through the end of study (eg, obeticholic acid, elafibranor, and cenicriviroc) is prohibited.

The following medications are prohibited for all treatment groups, from 30 days prior to Day 1 and through the end of study:

- Any medication or supplement prescribed for weight loss.

- Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters OATP1B1 or 1B3, potent or moderate inducers of CYP2C8, or potent inducers of CYP3A4) with study 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 should be used with caution are listed below in Table 5-3**.**

Table 5-3. List of Representative Disallowed and Use with Caution Medications[a]

Disallowed 30 days prior to Day 1 through the End of Treatment
Chronic systemic corticosteroids[b], tacrolimus, sirolimus, cyclosporine, mycophenolate mofetil, infliximab, and methotrexate
H2-Receptor antagonists[c]
azithromycin, clarithromycin, erythromycin
phenobarbital, phenytoin, carbamazepine, oxcarbazepine
rifamycins, isoniazid
Bosentan
St. John's Wort, Echinacea, milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Other[d]: gemfibrozil, modafinil
Agents to be used with Caution from 30 days prior to Day 1 through End of Treatment
antacids[e]
cholestyramine, colestipol, colesevelem[f]

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 H2 Receptor antagonists can be taken up to 3 days prior to Day 1.
d May result in an increase or decrease in the concentration of study drugs.
e 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.
f Bile acid sequestrants are permitted but may not be taken within 4 hours (before or after) oral study drug administration.

5.7. Accountability for Deuterated Water and Investigational Medicinal Product (IMP) and Devices

The investigator is responsible for ensuring adequate accountability of all used and unused deuterated water, study drug, kits, and devices. This includes acknowledgement of receipt of each shipment of deuterated water, study drug and/or devices (quantity and condition). All used and unused deuterated water, study drug and/or devices dispensed to subjects must be returned to the site.

IMP and device accountability records will be provided to each study site to:

- Record the date received and quantity of deuterated water, study drug and/or devices
- Record the date, subject number, deuterated water, study drug lot/kit number and/or devices dispensed
- Record the date, quantity of used and unused deuterated water, study drug and/or devices returned, along with the initials of the person recording the information.

5.7.1. Investigational Medicinal Product and Device Return or Disposal

Study drug return disposal will be performed as outlined in Section 9.1.8.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject screened and/or enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to Enrollment and throughout the study.

Documentation of the personally signed and dated informed consent of each subject, using the study-specific ICF, is required before initiating the Screening process.

After written informed consent has been obtained and eligibility to participate established, investigative site personnel will obtain the subject's identification number and study drug assignment from the interactive web response system (IWRS).

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

6.2. Screening Assessments

6.2.1. Screening Visit

Subjects will be screened within 2 weeks prior to Day -14 to determine eligibility for participation in the study. The Screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences, Inc.

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the Screening Visit to ensure an approximate 10-hour fast prior to the fasting blood sample collection the next morning.

The following will be performed and documented during the Screening period:

- Obtain written informed consent before initiation of any Screening procedures
- Review and record whether the subject has met inclusion and exclusion criteria
- Obtain Screening number from IWRS
- Obtain medical history including, but not limited to, information related to the following: type 2 diabetes mellitus, NAFLD, and NASH

- Review of historical liver biopsy report (if applicable) obtained within the last 6 months of the date of the Screening Visit.
- Complete physical examination including vital signs, body weight, and height
- Perform fundus exam with pharmacological pupil-dilation or digital fundus photography specified for non-dilated examination (For subjects with type 2 diabetes diagnosed prior to the date of the Screening Visit OR on Screening Visit labs (defined as HbA1c ≥6.5% only). If a fundus exam matching this description has been performed within 90 days prior to the date of the Screening Visit, the procedure does not need to be repeated, unless there has been worsening of visual function since the historical fundus exam in the opinion of the investigator.)
- Conduct standard 12-lead ECG
- Perform MRI-PDFF (Historical MRI-PDFF within 4 weeks of the date of the Screening Visit acceptable)
- Perform MRE (Historical MRE within 4 weeks of the date of the Screening Visit acceptable)
- Perform FibroScan® (Historical FibroScan® within 4 weeks of the date of the Screening Visit acceptable)
- Collect blood samples for:

  Chemistry and hematology

  Coagulation Panel

  Insulin and Lipids

  Hemoglobin A1c

  eGFR

  HIV-1, HBV & HCV Serology

  Calcitonin

  ELF™ Test

  FibroTest®

  CCI [redacted]

  Serum pregnancy test (only for female subjects of childbearing potential)

- Collect urine samples for:

  Drug screen

  CCI [redacted]

- Record any serious adverse events (SAEs) and all adverse events (AEs) related to protocol mandated procedures occurring after signing of the informed consent form.

- Record all concomitant medications that the subject has taken within 30 days prior to the date of the Screening Visit.

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

After review of the inclusion and exclusion criteria to confirm eligibility, subjects will return to the site for Enrollment and the initiation of Kinetic Biomarkers Cycle 1 on Day -14.

6.3. Pretreatment Assessments

6.3.1. Day -14 Visit

After review of inclusion and exclusion criteria to confirm continued eligibility, subjects will be enrolled via IWRS.

Subjects returning to the clinic for Enrollment on Day -14 should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. The following assessments will be performed and documented at the visit:

- Review and record whether the subject has met eligibility criteria

- Update medical history if a change has occurred during the Screening period

- Symptom driven physical examination

- Record vital signs and body weight

- Collect blood samples (prior to deuterated water administration):

  Chemistry and Hematology

  Coagulation panel

eGFR

Kinetic Biomarkers

- Collect urine samples (prior to deuterated water administration):

  Kinetic Biomarkers

- Dispense deuterated water. Subjects will drink approximately 45 mL of deuterated water three times per day starting on Day -14 through Day -8. The first dose of deuterated water will be administered under the supervision of investigative site personnel and monitored for at least 30 minutes after for any side effects.

- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring since the previous visit.

- Record all concomitant medications that the subject has taken since the previous visit.

Refer to the laboratory manual for additional information on the Kinetic biomarkers assessments.

6.3.2. Day -11 and Day -7 Visits (± 1 day)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning.

The following assessments will be performed and documented at each visit:

- Collect blood samples:

  Kinetic Biomarkers

- Collect urine samples:

  Kinetic Biomarkers

- Subjects will continue to drink deuterated water three times per day through Day 8.

- Review deuterated water compliance (Day -7 only)

- Record any serious adverse events and all adverse events related to protocol mandated procedures since the previous visit.

- Record all concomitant medications that the subject has taken since the previous visit.

Refer to the laboratory manual for additional information on the Kinetic Biomarkers assessments.

6.4. Treatment Assessments

6.4.1. Day 1 Visit

Subjects will be randomized to study drug assignment via IWRS.

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. The following assessments will be performed and documented at the Day 1 Visit prior to dosing:

- Symptom driven physical examination
- Record vital signs and body weight
- QoL questionnaires (CLDQ-NAFLD, EQ-5D)

  Note: It is recommended that the questionnaires be completed prior to any study procedures being performed and prior to the subject seeing a health care provider.
- Subjects with type 2 diabetes must be instructed to measure their blood glucose in connection with symptoms of hypoglycemia from the Day 1 Visit through the Telephone Follow-Up Visit. Plasma glucose values ≤70 mg/dL (≤3.9 mmol/L) should be reported to the site as a hypoglycemic episode. Hypoglycemic episodes must be reported as an AE in the AE form. If the hypoglycemic episode fulfills the serious criteria, the event must be reported in the eCRF database and to Gilead PVE as an SAE.
- Calculate CP Score once central laboratory results are available
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  Insulin and Lipids

  eGFR

  CCI [redacted]

  Kinetic Biomarkers

CCI [redacted]

- Collect urine samples:

  Urine pregnancy test (only for female subjects of childbearing potential)

  CCI [redacted]

  Kinetic Biomarkers

- Dispense study drugs, and provide subject with dosing instruction on appropriate dosing and administration; subject will take the Day 1 dose of study drugs on-site
- Record any SAEs and all AEs related to protocol mandated procedures occurring since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

6.4.2. Day 7 (Week 1) Visit (± 3 days)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. Subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at this visit:

- Symptom driven physical examination
- Record vital signs and body weight
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  eGFR

  Single PK sampling anytime during the visit

- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit

6.4.3. Day 28 (Week 4) Visit (± 3 days)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the visit:

- Symptom driven physical examination
- Record vital signs and body weight
- Calculate CP Score once central laboratory results are available
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  Insulin and Lipids

  eGFR

  Single PK sampling anytime during the visit
- Collect urine samples for:

  Urine pregnancy test (only for female subjects of childbearing potential)
- Review study drug dosing compliance
- Dispense study drugs
- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit

6.4.4. Day 56 (Week 8) Visit (± 3 days)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the visit:

- Symptom driven physical examination
- Record vital signs and body weight
- Calculate CP Score once central laboratory results are available
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  Insulin and Lipids

  eGFR

  Single PK sampling anytime during the visit
- Collect urine samples for:

  Urine pregnancy test (only for female subjects of childbearing potential)
- Review study drug dosing compliance
- Dispense study drugs
- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit

6.4.5. Day 84 (Week 12) Visit (± 3 days)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the visit:

- Symptom driven physical examination
- Record vital signs and body weight
- Perform MRI-PDFF

- Perform MRE
- Perform FibroScan®
- Calculate CP Score once central laboratory results are available
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  Insulin and Lipids

  Hemoglobin A1c

  eGFR

  FibroTest®

  ELF™ Test

  CCI [redacted]

  Single PK sampling anytime during the visit

- Collect urine samples for:

  Urine pregnancy test (only for female subjects of childbearing potential)

  CCI [redacted]

- QoL questionnaires (CLDQ-NAFLD, EQ-5D)

  Note: It is recommended that the questionnaires be completed prior to any study procedures being performed and prior to the subject seeing a health care provider.

- Review study drug dosing compliance
- Dispense study drugs
- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit

6.4.6. Day 112 (Week 16) Visit (± 3 days)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the visit:

- Symptom driven physical examination
- Record vital signs and body weight
- Calculate CP Score once central laboratory results are available
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  eGFR
- Collect urine samples for:

  Urine pregnancy test (only for female subjects of childbearing potential)
- Review study drug dosing compliance
- Dispense study drugs
- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit

6.4.7. Day 140 (Week 20) Visit (± 3 days)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the visit:

- Symptom driven physical examination
- Record vital signs and body weight
- Calculate CP Score once central laboratory results are available
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  eGFR
- Collect urine samples for:

  Urine pregnancy test (only for female subjects of childbearing potential)
- Review study drug dosing compliance
- Dispense study drugs
- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit

6.4.8. Day 154 (Week 22) Visit (± 1 day)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

Subjects will complete one additional cycle of Kinetic Biomarkers from Day 154 through Day 160 (Cycle 2).

The following assessments will be performed and documented at the visit:

- Collect blood samples for (prior to dose of deuterated water administration):

  Kinetic Biomarkers
- Collect urine samples (prior to dose of deuterated water administration):

  Kinetic Biomarkers

- Dispense deuterated water. Subjects will drink approximately 45 mL of deuterated water three times per day starting on Day 154 through Day 160. The first dose of deuterated water in Cycle 2 will be administered under the supervision of investigative site personnel and monitored for at least 30 minutes after for any side effects.

- Record all concomitant medications that the subject has taken since the previous visit

- Record any SAEs / AEs since the previous visit

6.4.9. Day 157 (Week 22 Day 2) and Day 161 (Week 23) Visit (± 1 day)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the visit:

- Collect blood samples for:

  Kinetic Biomarkers

- Collect urine samples:

  Kinetic Biomarkers

- Subjects will continue to drink deuterated water three times per day through Day 160.

- Review deuterated water compliance (Day 161 (Week 23) only)

- Record all concomitant medications that the subject has taken since the previous visit

- Record any SAEs / AEs since the previous visit

6.4.10. Day 168 (Week 24) / End of Treatment Visit (± 3 days)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the visit:

- Symptom driven physical examination

- Record vital signs and body weight
- Conduct standard 12-lead ECG
- Perform MRI-PDFF
- Perform MRE
- Perform FibroScan®
- Calculate CP Score once central laboratory results are available
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  Insulin and Lipids

  Hemoglobin A1c

  eGFR

  FibroTest®

  ELF™ Test

  CCI [redacted]

  Kinetic Biomarkers

- Collect urine samples for:

  Urine pregnancy test (only for female subjects of childbearing potential)

  CCI [redacted]

  Kinetic Biomarkers

- QoL questionnaires (CLDQ-NAFLD, EQ-5D)

  Note: It is recommended that the questionnaires be completed prior to any study procedures being performed and prior to the subject seeing a health care provider.

- Dispense urine pregnancy testing kit and provide instructions for home testing at the Telephone Follow-Up visit (only for female subjects of childbearing potential).

- Review study drug dosing compliance.
- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit

6.4.11. Early Termination (ET) Visit

Subjects prematurely discontinuing from the study should complete an ET visit within 30 days of last dose of study drugs or pretreatment deuterated water.

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the visit:

- Symptom driven physical examination
- Record vital signs and body weight
- Conduct standard 12-lead ECG
- Perform MRI-PDFF (at the discretion of the investigator)
- Perform MRE (at the discretion of the investigator)
- Perform FibroScan® (at the discretion of the investigator)
- Calculate CP Score once central laboratory results are available
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

  eGFR

  Insulin and Lipids (at the discretion of the investigator)

  Hemoglobin A1c (at the discretion of the investigator)

  FibroTest® (at the discretion of the investigator)

  ELF™ Test (at the discretion of the investigator)

CCI [redacted]

- Collect urine samples for:

  Urine pregnancy test (only for female subjects of childbearing potential)

  CCI [redacted]

- Dispense urine pregnancy testing kit and provide instructions for home testing at the Telephone Follow-Up visit (only for female subjects of childbearing potential).
- Review study drug dosing compliance
- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit

6.4.12. Unscheduled Visits

Additional unscheduled assessments may be performed at the discretion of the investigator. At a minimum, the following will be performed and documented.

- Symptom driven PE
- Record vital signs, and body weight
- Collect blood samples for:

  Chemistry and Hematology

  Coagulation panel

- Record all concomitant mediations that the subject has taken since the previous visit
- Record any SAEs / AEs since the previous visit
- 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. Posttreatment Assessments

6.5.1. Telephone Follow-Up Visit (± 3 days)

Subjects that received at least one dose of study drug will be contacted for a Telephone Follow-Up Visit 7 weeks after the date of the last dose of study drugs.

The following assessments during the Telephone Follow-Up visit:

- Record all concomitant medications that the subject has taken since previous study visit

- Record any SAEs / AEs since the previous visit
- Record subject reported results of the urine pregnancy test (only for female subjects of childbearing potential).

At the discretion of the investigator, an unscheduled visit may be completed if the subject reports abnormal or concerning symptoms.

Table 6-1. Visit Windows

Study Visit	Window
Screening Visit	≤ 2 weeks prior to Day -14, window begins with the signing of the informed consent*
Day -14	Day of enrollment and first dose of deuterated water
Day -11 & Day -7	± 1 day
Day 1	Day of randomization and first dose of study drugs. All on-treatment study visits are calculated based on the Day 1 date
Day 7 (Week 1), Day 28 (Week 4), Day 56 (Week 8), Day 84 (Week 12), Day 112 (Week 16) & Day 140 (Week 20)	± 3 days
Day 154 (Week 22), Day 157 (Week 22 Day 2) & Day 161 (Week 23)	± 1 day
Day 168 (Week 24/EOT)	± 3 days
ET Visit	Within 30 days of last dose of study drug or pre-treatment deuterated water
Telephone Follow-Up Visit	± 3 days

* The Screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences, Inc.

6.6. Criteria for Discontinuation of Study Treatment

Study drug may be discontinued in the following instances:

- Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
- Diagnosis of acute pancreatitis
- Diagnosis of medullary thyroid carcinoma
- Surgical treatment for obesity
- Treatment with other GLP-1 receptor agonists other than semaglutide

- Subject progression to decompensated cirrhosis, as defined by any of the following:

  Clinically apparent ascites requiring treatment

  HE of Grade 2 or above (according to the West Haven criteria in Appendix 5) requiring treatment.

  Portal hypertension-related upper gastrointestinal bleeding identified by endoscopy and requiring hospitalization, including events of bleeding from esophageal varices, gastric varices, and portal hypertensive gastropathy.

- CP score ≥ 7 on two consecutive occasions at least two weeks apart unless due to an alternate etiology (e.g., therapeutic anticoagulation); refer to Section 7.6.3.
- Liver transplantation
- Subject develops an SAE consisting of a serious hypersensitivity reaction to study drug
- 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 subject may resume study dosing at the discretion of the Investigator, in consultation with the Medical Monitor.
- Unacceptable toxicity or toxicity that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Subject or Investigator request to discontinue for any reason.
- Significant subject noncompliance.
- Significant protocol violation that impacts subject safety.
- Pregnancy during the study; refer to Appendix 3
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB.

6.7. Assessments for Premature Discontinuation from Study

It is recommended that subjects who discontinue study drugs be encouraged to stay on study and complete the scheduled assessments. Subjects prematurely discontinuing from the study (eg, due to subject withdrawing consent, investigator decision, or sponsor decision) should complete an ET visit within 30 days of last dose of study drugs or pretreatment deuterated water. Subjects that received at least one dose of study drug will be contacted for a Telephone Follow-up Visit 7 weeks after the date of the last dose (refer to Section 6.4.10). Discussion with the Medical Monitor prior to discontinuation of study drug or study is recommended

If a subject is lost to follow-up, survival data may be gathered from public records such as government census or death records (if permitted by local regulations) prior to the completion of the study.

6.8. Interruption of Study Drug

If dosing is interrupted (i.e., as a result of an AE), the subject must stop dosing of all study drugs. Every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures. Discussion with the Medical Monitor is recommended. If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study.

6.9. End of Study

End of study is considered to be completion of the Telephone Follow-Up visit.

6.10. Description of Assessments

6.10.1. Clinical Laboratory Analytes

Fasting is required prior to all study visits.

Chemistry:

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase (ALP), bicarbonate, blood urea nitrogen (BUN),) creatine kinase (CPK), calcium, chloride, creatinine, glucose, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, and gamma-glutamyl transferase (GGT).

Hematology:

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

Coagulation Panel:

INR, prothrombin time (PT), partial thromboplastin time (PTT).

Insulin and lipids:

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

Pregnancy Tests:

Serum β-hCG or urine β-hCG (if positive, requires immediate confirmation with serum β-hCG).

Additional Tests:

HIV-1 (reflex to HIV-1 RNA), HBV (HBsAg), HCV (reflex to HCV RNA) serology, urine drug screen (for amphetamines, cocaine, methadone, opiates), eGFR as calculated by MDRD, HbA1c, calcitonin, genomic sample collection, ELF™ Test, and FibroTest®.

Pharmacokinetic (PK) Assessments:

Single PK samples may also be used to measure protein-binding of study drug(s) and/or its metabolites, as applicable.

Biomarker Tests:

CCI [redacted]

Kinetic Biomarker Assessments

6.10.2. Creatinine Clearance/eGFR

eGFR is estimated by creatinine clearance calculated by as calculated by the Modification of Diet in Renal Disease (MDRD) Study equation:

> eGFR (mL/min/1.73 m^2) 175 × Serum $Creainine^{-1.154}$ × $(Age)^{-0.203}$ × (1.212 if African American) × (0.742 if female)

Serum creatinine in umol/L should be rounded to zero decimal places and converted to mg/dL by multiplying by 0.01131 prior to applying the formula. Creatinine in mg/dL is rounded to 2 decimal places prior to applying formula.

6.10.3. Child-Pugh (CP) Score

Child Pugh score is used to assess the prognosis of chronic liver disease, primarily cirrhosis. CP scores will be calculated by the site from the central laboratory values at each applicable visit.

Table 6-2. Child-Pugh Classification of the Severity of Cirrhosis

	1	2	3
Hepatic Encephalopathy (HE)	**None** No encephalopathy and not on any treatment for hepatic encephalopathy	**Medication-Controlled** Subject is lethargic, may have moderate confusion Subject 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** Cross sectional imaging showing ascites Abdominal distension Medication for ascites	**Severe (diuretic-refractory)** Visible clinically
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

CP score is obtained by adding the score for each parameter.
CP class:
- A 5 6 points
- B 7 9 points
- C 10 15 points

Records of concomitant medications for ascites and HE will be collected in the eCRF.

6.10.4. MRE and MRI-PDFF

The sites will perform liver stiffness assessments by MRE (shear wave 60 Hz) and MRI-PDFF at the Screening Visit, Day 84 (Week 12) and Day 168 (Week 24). For ET visits, the assessments are performed at the discretion of the investigator. The assessments can occur sequentially.

At least 4 hours fasting is recommended prior to all MR assessments. The MRE and MRI-PDFF scans will be read by a central reader. If the Day 84 (Week 12), Day 168 (Week 24) or ET visits MRE CCI [redacted]

Please refer to the MR Procedures Manual for instructions on MRE and MRI-PDFF measurements.

6.10.5. FibroScan®

FibroScan® examinations will be performed at the Screening Visit, Day 84 (Week 12) and Day 168 (Week 24) and median liver stiffness in kilopascals (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 interquartile range of CAP values will be recorded from FibroScan® examinations. For ET visits, the assessments are performed at the discretion of the investigator.

For individual subjects, the same device must 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 XL probe should be used at all exams if available. If an XL probe is not available and/or a valid result cannot be obtained, an examination with the M probe must be performed and the result recorded. At least 2-3 hours fasting is recommended prior to all elastography assessments.

6.10.6. Electrocardiogram

Standard 12-lead electrocardiogram (ECG) assessments will be performed at Screening, Day 168 (Week 24) and the Early Termination (ET) visits. The Investigator will review the ECGs for any clinically significant abnormalities to ensure subject 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.

6.10.7. Medical History

Medical history, including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history will be collected on all subjects during the Screening period.

6.10.8. Physical Examination

A complete physical examination must 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. Height, vital signs, and body weight will also be collected.

The focus of a symptom driven PE will be determined by the investigator based on subject complaints. For example, if a subject complains of a cough, a lung exam should be performed. If consistent with pneumonia (rales/crackles on exam) then an AE would be documented.

Height and body weight will be collected at specified time points.

6.10.9. Fundus Examination

For subjects with type 2 diabetes (from medical history or from Screening Hemoglobin A1c ≥6.5%), a fundus exam will be performed at Screening. Fundus examinations require pharmacological dilation of both pupils or the use of a digital fundus photography camera specified for non-dilated examination. Results of the fundus exam will be evaluated by the investigator and the investigator evaluation must be documented either on the fundus examination result report or in the subject's medical record.

The investigator or medically qualified delegate must sign, date and interpret the fundus examination by using the following categories:

- Normal
- Abnormal

  Was the result clinically significant? (Yes/No)

If a fundus examination matching this description has been performed within 90 days prior to the date of the Screening Visit, 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 Enrollment (Day -14).

If the dilated fundus examination is performed before the subject has signed the informed consent form, it must be documented in the medical records that the reason for performing the procedure was not related to this trial.

6.10.10. Vital Signs

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

Blood pressure will be measured using the following standardized process:

- Subject 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 mmHg mark on the manometer or to the nearest whole number on an automatic device.

6.10.11. Pregnancy Testing

All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 (prior to dosing), Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24 (EOT) or ET visits. All females of childbearing potential that received at least one dose of study drug will be dispensed a urine pregnancy testing kit at the Week 24 (EOT) or ET visit for home testing at the Telephone Follow-Up visit. At the Telephone

Follow-Up visit, subjects will be requested to report the result of the urine pregnancy tests. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drug immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

6.10.12. Health Related Quality of Life (HRQoL) Measures

It is recommended that these questionnaires be completed prior to the clinical and laboratory assessments. The subject should read the questionnaires by himself/herself and record the answers by himself/herself.

6.10.12.1. Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease (CLDQ-NAFLD)

The CLDQ-NAFLD asks questions related to liver disease and specifically NAFLD, to measure health related quality of life in subjects with chronic liver disease.

6.10.12.2. EuroQol Five Dimensions (EQ-5D)

The EQ-5D questionnaire is a standard measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economical appraisal {The EuroQol Group 1990}. The EQ-5D is not disease specific and has been validated in numerous health states. The tool consists of the EQ-5D descriptive system and the EQ Visual Analog Scale (VAS). The descriptive part comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each of these 5 dimensions has 5 levels (no problem, slight problems, moderate problems, severe problems and unable to). Results for each of the 5 dimensions are combined into a 5-digit number to describe the subject's health state. The VAS records the subject's health on a 0-100 mm VAS scale, with 0 indicating "the worst health you can imagine" and 100 indicating "the best health you can imagine".

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, 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 medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or posttreatment complications that occur as a result of protocol specified procedures or special situations (Section 7.7). Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

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 adverse event and must be reported.
- Pre-existing 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 (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject 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 was more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- 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 subject 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;

Development of drug dependency or drug abuse.

- A hypoglycemic episode is considered an SAE if it meets a criteria above or it requires the assistance of another person to correct (e.g., to administer carbohydrate).

For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and reported as a SAE.

7.1.2.1. Events of Special Interest

Hypoglycemic episodes must be reported as an AE in the AE form. For subjects without T2D, episodes must be reported in accordance with Section 7. Subjects with T2D 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 and other relevant clinical data must be reported on a hypoglycemic episode form in the eCRF. If the hypoglycemic episode fulfills the serious criteria, the event must be reported in the eCRF database and to Gilead PVE as an SAE.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

- **No**: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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

The relationship of an AE or SAE to study procedures (eg, invasive procedures such as venipuncture or biopsy) or study devices (eg, PDS290 pen-injector) should be assessed using clinical judgement describing the event as either unrelated (No) or related (Yes) consistent with the following definitions:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure or device.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture) or device.

7.2.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, 4, or 5 according to the Common Terminology Criteria for Adverse Events (CTCAE), which can be found in the Site Operations Manual and Appendix 4.

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.

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form eCRF: all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, through 7 weeks after last administration of study drug, must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences, Inc may request that certain AEs are followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required posttreatment Follow-Up period, must be reported to the eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the posttreatment Follow-Up visit but within 7 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 study participation has concluded and the event is deemed relevant to the use of study drug or device, he/she should promptly document and report the event to Gilead Pharmacovigilance and Epidemiology (PVE).

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

- At the time of study start, SAEs may be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead Sciences PVE:	Fax:	PPD
	Email:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject 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 subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs).

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

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

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and 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, electrocardiogram, 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).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Sections 7.1 and 7.6.

Severity should be recorded and graded according to the CTCAE Toxicity Grading Scale (Appendix 4). For AEs associated with laboratory abnormalities, the event should be graded on 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.

7.6. Toxicity Management

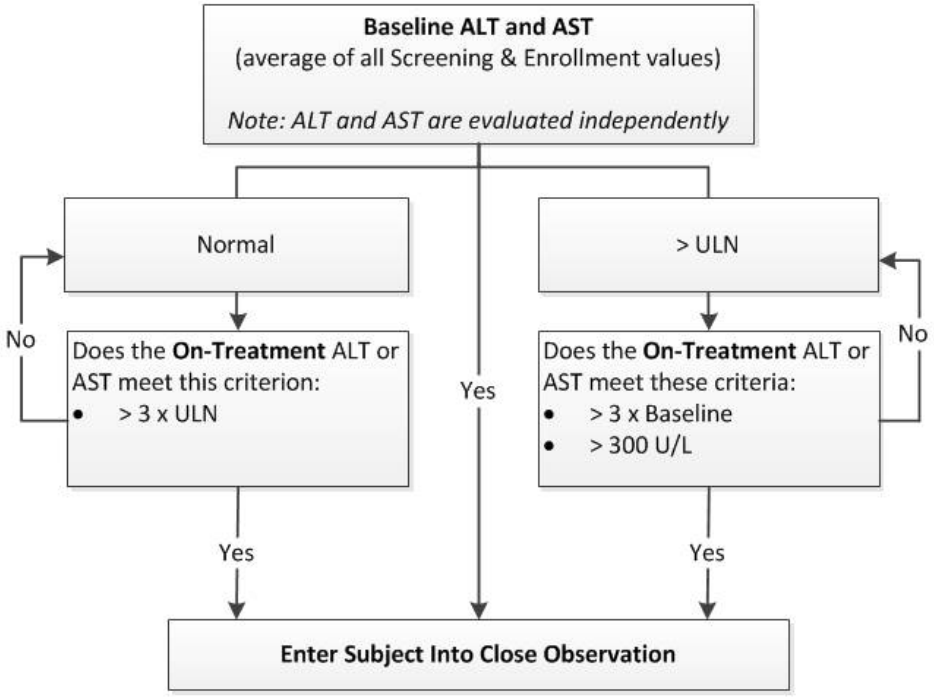
7.6.1. Observation for Drug Induced Liver Injury (DILI)

At baseline, some subjects may have liver biochemistry levels above the upper limit of the normal range (ULN). Baseline values for liver tests (ALT, AST, and total bilirubin) will be determined by averaging the values obtained between and including Screening and Enrollment (Day -14). Please refer to the Covance Laboratory Manual or individual subject Covance laboratory report for gender and age specific reference ranges.

Unless the clinical context points towards an apparent etiology, on-treatment elevations of ALT and/or AST should be confirmed with repeat testing within 72 hours of results. If the results are confirmed, and if no other cause of the laboratory abnormalities is immediately apparent, notify the Medical Monitor.

Subjects with repeat ALT or AST elevations as per Figure 7-1 subjects must be placed into close observation (as described below).

Figure 7-1. On-Treatment ALT/AST Monitoring Requiring Close Observation



7.6.2. Close Observation

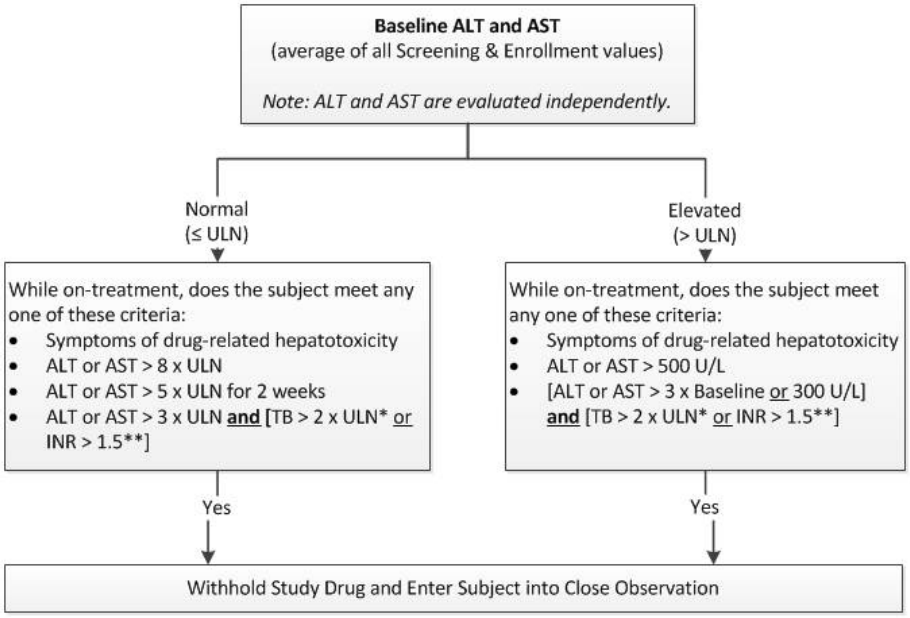
Close observation includes:

- Repeating liver biochemistries (ALT, AST, ALP, GGT, total bilirubin, INR) and obtaining a CPK level within 72 hours of results
- Obtaining a more detailed history of symptoms and prior or concurrent disease
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtaining a history of exposure to environmental chemical agents
- Ruling out other causes of liver disease as needed (obtain viral hepatitis panel, imaging for evaluation of biliary tract disease, etc. if required in the opinion of the Investigator)
- Continue to monitor liver biochemistries at least twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study drugs have been discontinued and the subject is asymptomatic

During a period of close observation for DILI, study drugs can be continued, if desired, at the discretion of both the Medical Monitor and Investigator.

If on-treatment elevations of ALT and/or AST exceed the values shown in Figure 7-2, are confirmed on repeat testing within 72 hours of results, and no alternative cause is immediately apparent, the subject must be placed into close observation and all three study drugs must be withheld.

Figure 7-2. On-Treatment Monitoring Requiring Withholding of Study Drugs



* Unless subject has Gilbert's syndrome, in which case a direct bilirubin > 2 x baseline (average of Screening & Enrollment values) will be used instead of total bilirubin.
**If not on therapeutic anticoagulation (e.g. warfarin). If on therapeutic anticoagulation, INR criteria is disregarded.

Abbreviations:
ULN – Upper limit of normal range
TB – Total Bilirubin

If study drugs are withheld, they may be reintroduced with approval from the Gilead Medical Monitor.

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

Other than in the case of the liver enzymes noted above, Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and

preferably within 3 calendar days of receipt of the original test results. 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.

Any questions regarding toxicity management should be directed to the Medical Monitor.

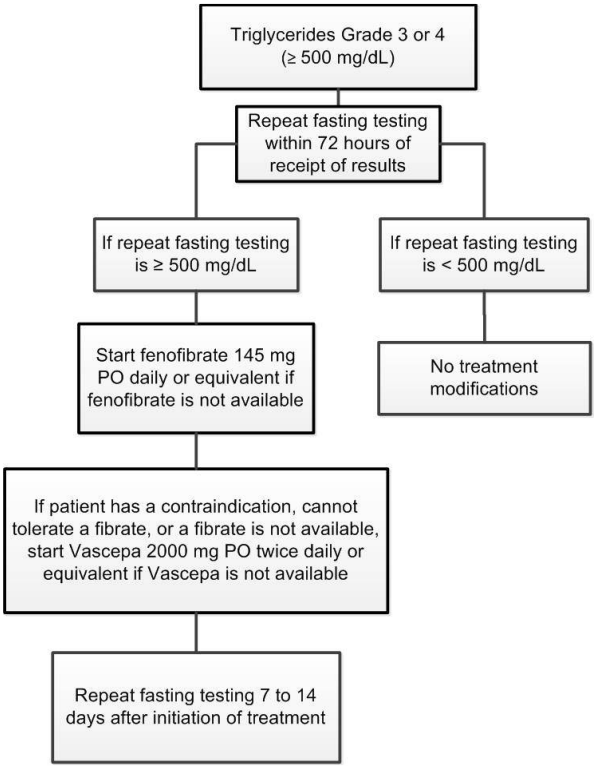
7.6.3. CP Score

If a subject has an increase in their CP score to ≥ 7, this should be confirmed with repeat testing within 72 hours of receipt of results. If confirmed, the Medical Monitor should be notified and the subject should be placed in close observation described above, unless an alternate etiology (eg, therapeutic anticoagulation) is identified. If the CP remains ≥ 7 for 2 consecutive weeks, and an alternate etiology has not been identified, study drugs must be discontinued.

7.6.4. Hypertriglyceridemia

Although some randomized subjects will have baseline dyslipidemia, some subjects may experience further elevations in their triglycerides. Figure 7-3 describes the recommended monitoring and intervention strategy for subjects that meet the criteria for on-treatment hypertriglyceridemia of Grade 3 or 4 (≥ 500 mg/dL).

Figure 7-3. Algorithm for Monitoring and Treatment of Hypertriglyceridemia



7.6.5. Pruritus Management

The development or worsening of pruritus during the study is a consideration for patients 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 the study drug dosing, as described in Table 5-3. Administration of study drugs with a light-fat meal may be beneficial. If interruption of study drugs is deemed necessary, all study drugs must be held (see Section 6.9). There is no option for dose reduction.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE, and pregnancy reports regardless of an associated AE, and AE in an infant following exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product 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 medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one’s professional or non-professional occupation.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug and throughout the study, including the post study drug Follow-Up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Reports should be sent directly to Gilead PVE at fax number PPD or email PPD

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. 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 Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the pregnant partner should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report 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.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of study drug(s) in subjects with NASH

CCI [redacted]

8.1.2. Primary Endpoint

The primary endpoint is the safety and tolerability of study drug(s) in subjects with NASH.

CCI [redacted]

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

Subjects who receive study drugs other than that to which they were assigned will be analyzed according to the treatment group to which they were randomized.

8.2.1.2. Safety

The primary analysis set for safety analyses will include all subjects who received at least one dose of study drug. Treatment-emergent data will be analyzed and defined as data collected from the first dose of study drug through the date of last dose of study drug plus 30 days. Subjects who received study drug other than that to which they were assigned will be analyzed according to the study drug received.

8.2.1.2.1. Pharmacokinetics

The PK analysis set will include all randomized subjects who took at least one dose of study drug and have at least 1 nonmissing postdose concentration value for the corresponding analyte in plasma.

CCI [redacted]

8.2.2. Interim Analysis

Administrative interim analyses may be performed during the study to support publications or interactions with regulatory agencies.

8.3. Data Handling Conventions

Missing data can have an impact on the interpretation of the trial data. In general, values for missing data will not be imputed.

Where appropriate, safety data for subjects that did not complete the study will be included in summary statistics. For example, if a subject received study drug, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed, then they will be excluded from the summary. If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a pre-dose value, then the subject will be excluded from the calculation of summary statistics for the pre-dose value and the change from pre-dose values.

Values for missing safety laboratory data and vital signs will not be imputed; however, a missing baseline result will be replaced with a Screening result, if available. If no pre-treatment 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.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment group and overall. Demographic summaries will include sex, race, ethnicity, and age.

Baseline characteristics summary will include body weight, height, body mass index, presence or absence of type 2 diabetes, and other disease characteristics as necessary.

8.5. Efficacy Analysis

The biological activity of study drug(s) will be evaluated using radiologic endpoints and biomarker variables. Because efficacy endpoints will be evaluated for exploratory purpose, formal statistical comparisons will not be made for these endpoints. Instead, descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment group.

CCI [redacted]

[redacted]

8.6. Safety Analysis

Safety will be assessed by clinical laboratory tests and vital signs measurements at various time points during the study, and through the documentation of AEs.

All safety data collected on or after the first dose of study drug administration (up to and including 30 days after the last dose of study drug) will be summarized by treatment group according to the study drug received.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database. Adverse event severity will be graded using CTCAE.

Events will be summarized on the basis of the date of onset for the event. Treatment-emergent adverse events (TEAEs) are 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 30 days after permanent discontinuation of study drug.
- Any AEs leading to premature discontinuation of study drug.

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

All AEs reported during the study will be presented in data listings with TEAE indicated (yes/no).

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, 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 one toxicity grade from baseline at any time post-baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

8.7. Pharmacokinetic Analysis

Plasma concentrations of study drug(s) and relevant metabolites, as applicable, will be listed.

8.7.1. Other Safety Evaluations

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

8.8. Biomarker Analysis

The kinetic biomarkers will be analyzed to evaluate the PD effects of study drug(s). The assessment will involve the analysis of DNL values; specifically, the change (absolute and relative) from baseline between the post-dose and pre-dose deuterated water loading periods.

CCI [redacted]

8.9. Sample Size

Due to the exploratory nature of this study, the sample size was not determined by any formal power calculation. The number of subjects in each treatment group was decided based on clinical experience with other similar proof of concept studies.

8.10. Data Monitoring Committee

An internal Gilead data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data. The DMC will be notified of any case of suspected DILI by the Medical Monitor. The DMC will provide recommendations whether the nature, frequency, and severity of adverse effects 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 the study should continue with modifications. The DMC's specific activities will be defined by a mutually agreed upon charter, which will define the DMC's membership, conduct, and meeting schedule.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonization (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The Investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The Investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under 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 Gilead 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 subject completes the protocol-defined activities.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under 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 Gilead 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 subject completes the protocol-defined activities.

9.1.3. Institutional Review Board (IRB) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB. The investigator will not begin any study subject activities until approval from the IRB 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 any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB approval, with the exception of those necessary to reduce immediate risk to study subjects.

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 and before undertaking any study-related procedures. The investigator must use the most current approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by local requirements). The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.5. Confidentiality

The investigator must assure that subjects' 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 the Sponsor, IRB or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject 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 investigator brochure, this protocol, eCRFs, the study drug, 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 two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, 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 subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject 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 adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including 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 until 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, United States, 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, until 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 subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the electronic data capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator 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 (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6

9.1.8. Investigational Medicinal Product Accountability and Return

Where possible, study drug should be destroyed at the site. If the site has an appropriate standard operating procedure (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 central files. If study drug is destroyed on 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 eventual destruction. The study monitor will provide instructions for return.

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

9.1.9. Inspections

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

9.1.10. 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 subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared. 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.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

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, e.g. attendance at Investigator's 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 trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

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 subject records needed to verify the entries on 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 of 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 Gilead medical monitor 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 Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

Gilead Sciences, Inc.
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Foster City, CA 94404 USA

STUDY ACKNOWLEDGEMENT

A Proof of Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Monotherapy and Combination Regimens in Subjects with Nonalcoholic Steatohepatitis (NASH)

GS-US-454-5533, Amendment 2, 22 October 2019

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

PPD

PPD

22-Oct-2019
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

Appendix 2. Study Procedures Table

		Pretreatment Period			Treatment Period												
		Kinetic Biomarkers (Cycle 1)										Kinetic Biomarkers (Cycle 2)					
	Screening	Day −14	Day −11 (±1d)	Day −7 (±1d)	Day 1	Day 7 (WK 1) (±3d)	Day 28 (WK 4) (±3d)	Day 56 (WK 8) (±3d)	Day 84 (WK 12) (±3d)	Day 112 (WK 16) (±3d)	Day 140 (WK 20) (±3d)	Day 154 (WK 22) (±1d)	Day 157 (WK 22 Day 2) (±1d)	Day 161 (WK 23) (±1d)	Day 168 (WK 24/EOT) (±3d)[a]	ET	Telephone Follow-Up[b] (±3d)
Clinical Assessments																	
Written Informed Consent	X																
Confirm Eligibility	X	X															
Medical History	X	X															
PE, Vital Signs including Weight[c]	X	X			X	X	X	X	X	X	X				X	X	
Fundus Examination[d]	X																
Height	X																
12 lead ECG	X														X	X	
Quality of Life Questionnaires					X				X						X		
Calculate CP Score					X		X	X	X	X	X				X	X	
Dispense Deuterated Water		X										X					

		Pretreatment Period			Treatment Period												
		Kinetic Biomarkers (Cycle 1)										Kinetic Biomarkers (Cycle 2)					
	Screening	Day −14	Day −11 (±1d)	Day −7 (±1d)	Day 1	Day 7 (WK 1) (±3d)	Day 28 (WK 4) (±3d)	Day 56 (WK 8) (±3d)	Day 84 (WK 12) (±3d)	Day 112 (WK 16) (±3d)	Day 140 (WK 20) (±3d)	Day 154 (WK 22) (±1d)	Day 157 (WK 22 Day 2) (±1d)	Day 161 (WK 23) (±1d)	Day 168 (WK 24/EOT) (±3d)[a]	ET	Telephone Follow-Up[b] (±3d)
Dispense study drugs					X[e]		X	X	X	X	X						
Review of Deuterated Water Compliance				X										X			
Review of Study Drug Dosing Compliance							X	X	X	X	X				X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging Assessments																	
FibroScan®	X[g]								X						X	X[h]	
MRI PDFF, MRE	X[g]								X						X	X[h]	
Laboratory Assessments																	
Subject Fasting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry, Hematology, Coagulation	X	X			X	X	X	X	X	X	X				X	X	

		Pretreatment Period			Treatment Period												
		Kinetic Biomarkers (Cycle 1)										Kinetic Biomarkers (Cycle 2)					
	Screening	Day −14	Day −11 (±1d)	Day −7 (±1d)	Day 1	Day 7 (WK 1) (±3d)	Day 28 (WK 4) (±3d)	Day 56 (WK 8) (±3d)	Day 84 (WK 12) (±3d)	Day 112 (WK 16) (±3d)	Day 140 (WK 20) (±3d)	Day 154 (WK 22) (±1d)	Day 157 (WK 22 Day 2) (±1d)	Day 161 (WK 23) (±1d)	Day 168 (WK 24/EOT) (±3d)[a]	ET	Telephone Follow-Up[b] (±3d)
Insulin and Lipids	X				X		X	X	X						X	X[h]	
Hemoglobin A1c (HbA1c)	X								X						X	X[h]	
eGFR	X	X			X	X	X	X	X	X	X				X	X	
HIV 1, HBV, HCV Serology	X																
Calcitonin	X																
FibroTest®	X[g]								X						X	X[h]	
ELF™ Test[i]	X								X						X	X[h]	
CCI																	
Blood Collection (Kinetic Biomarkers)		X	X	X	X							X	X	X	X		
PK Sampling						X[j]	X[j]	X[j]	X[j]								
Pregnancy Testing[k]	X				X		X	X	X	X	X				X	X	X
Urine Drug Screen	X																

		Pretreatment Period			Treatment Period												
		Kinetic Biomarkers (Cycle 1)										Kinetic Biomarkers (Cycle 2)					
	Screening	Day −14	Day −11 (±1d)	Day −7 (±1d)	Day 1	Day 7 (WK 1) (±3d)	Day 28 (WK 4) (±3d)	Day 56 (WK 8) (±3d)	Day 84 (WK 12) (±3d)	Day 112 (WK 16) (±3d)	Day 140 (WK 20) (±3d)	Day 154 (WK 22) (±1d)	Day 157 (WK 22 Day 2) (±1d)	Day 161 (WK 23) (±1d)	Day 168 (WK 24/EOT) (±3d)[a]	ET	Telephone Follow-Up[b] (±3d)
CCI																	
Urine Collection (Kinetic Biomarkers)		X	X	X	X							X	X	X	X		
CCI																	

a Subjects prematurely discontinuing from the study should complete an ET visit within 30 days of last dose of study drugs or pretreatment deuterated water.
b Subjects that received at least one dose of study drug will be contacted for a Telephone Follow up Visit 7 weeks after the date of the last dose
c Complete physical examination to be performed at Screening. Symptom driven physical examination to be performed at Day 14, Day 1, Day 7 (Week 1), Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24 (EOT) or ET visits
d For subjects with type 2 diabetes (from medical history or from Screening Hemoglobin A1c ≥6.5%), a fundus exam will be performed at Screening. Fundus examinations require pharmacological dilation of both pupils or the use of a digital fundus photography camera specified for non dilated examination. If a fundus examination matching this description has been performed within 90 days prior to the date of the Screening Visit, 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 Enrollment (Day 14)
e Subject will take first dose of study drugs on site at Day 1.
f AE reporting during Screening is limited to SAEs and AEs related to study procedures
g Required for all subjects. Will not be used to assess eligibility for subjects that meet inclusion criteria based on historical liver biopsy. If a FibroScan® and/or MRE has been performed within 4 weeks prior to the date of the Screening Visit, the procedure does not need to be repeated. Similarly, if an MRI PDFF has been performed within 4 weeks prior to the date of the Screening Visit and is deemed acceptable by the central reader, the procedure does not need to be repeated
h At the discretion of the Investigator
i ELF™ Test score will not be provided to the sites
j Single PK sample anytime during visit
k All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 (prior to dosing), Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24 (EOT) or ET visits. All females of childbearing potential that received at least one dose of study drug will be dispensed a urine pregnancy testing kit at the Week 24 (EOT) or ET visit for home testing at the Telephone Follow Up visit. At the Telephone Follow Up visit, subjects will be requested to report the result of the urine pregnancy test

Appendix 3. 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 subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with 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 of any 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 subject of any age.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Cilofexor has not yet been studied in pregnant women. In the initial dose range-finding studies in pregnant mice and rabbits, there were no effects on embryofetal development other than a decrease in fetal body weights in pregnant rabbits administered 1000 mg/kg/day. The decrease in fetal body weights are likely secondary to maternal toxicity rather than a direct effect of cilofexor. The NOAEL for embryofetal development is 300 mg/kg/day in mice and 200 mg/kg/day in rabbits. These doses were associated with exposures that are > 50-fold higher than the anticipated human exposure at the maximum proposed human dose of 100 mg once daily. DDI data do not suggest a potential for interaction with hormones used for contraception. No formal studies have been conducted to evaluate the reproductive toxicity of firsocostat; therefore, the reproductive toxicity of firsocostat in humans is unknown. However, mutant mice lacking ACC1, one of the targets of firsocostat, are embryonically lethal. Therefore, firsocostat is contraindicated in pregnancy. Preclinical data in human hepatocytes indicate that firsocostat is a mild inducer of CYP3A4 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 firsocostat with hormonal contraceptives.

Semaglutide adversely affected embryo foetal 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 foetal 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. There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. Oral contraceptives are considered effective as no clinically relevant decrease in the overall exposure of ethinylestradiol and levonorgestrel was observed when co-administered with semaglutide s.c.

Please refer to the latest version of the corresponding Investigator's Brochure of each compound for additional information.

3) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to Enrollment unless permanently sterile or postmenopausal as defined in Appendix 3. Urine pregnancy tests will be performed at monthly intervals thereafter until week 24. A urine pregnancy testing kit will be dispensed at the Week 24 (EOT) or ET visit for home testing at the Telephone Follow-Up visit. Female subjects must agree to one of the following from Screening until 7 weeks following the last dose of study drug.

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

  Or

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

  Intrauterine device (IUD) with a failure rate of <1% per year

  Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year

  Tubal sterilization

  Essure® micro-insert system (provided confirmation of success 3 months after procedure)

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Should female subjects wish to use a hormonally based method, use of a male condom by the female subject's male partner is required. Subjects who utilize a hormonal contraceptive as one of their birth control methods must have used the same method for at least three months prior to study dosing. Hormonally-based contraceptives permitted for use in this protocol are as follows:

Oral contraceptives (either combined or progesterone only)

Injectable progesterone

Implants of levonorgestrel

Transdermal contraceptive patch

Contraceptive vaginal ring

Not all of these methods may be approved in each of the countries where the study is being conducted: please refer to local product information. Additional local regulatory requirements may apply.

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 7 weeks after the last dose of study drug.

4) Contraception Requirements for Male Subjects

- It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject’s seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until 7 weeks after the last dose of study drug. Female partners of male study subjects are asked to select one of the above methods.

- Male subjects must also refrain from sperm donation during treatment and until at least 7 weeks after the last dose of study drug.

5) Unacceptable Birth Control Methods

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

6) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 7 weeks of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is within 7 weeks of last study drug dose must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE)

Refer to the Site Operations Manual for additional CTCAE information.

Appendix 5. 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 three of the followings 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 three 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}