CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib, GS-0976, GS-9674, and Combinations in Subjects with Bridging (F3) Fibrosis or Compensated Cirrhosis (F4) due to 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:	NCT03449446	
Indication:	Nonalcoholic Steatohepatitis	
Protocol ID:	GS-US-454-4378	
Gilead Study Director	Name:	PPD
	Telephone:	PPD
	Fax:	PPD
	Email:	PPD
Gilead Medical Monitor:	Name:	PPD
	Telephone:	PPD
	Fax:	PPD
	Email:	PPD
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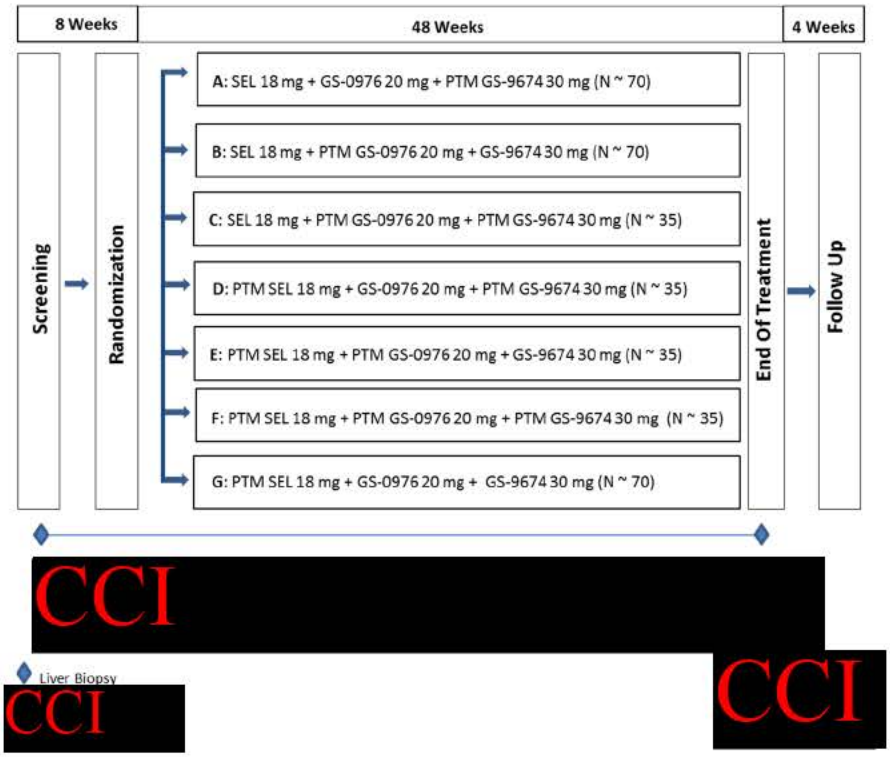
PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404 USA

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib, GS-0976, GS-9674, and Combinations in Subjects with Bridging (F3) Fibrosis or Compensated Cirrhosis (F4) due to Nonalcoholic Steatohepatitis (NASH)
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	141683 Not Applicable NCT03449446
Study Centers Planned:	Approximately 135 centers in the United States, Canada, Australia, New Zealand, and Hong Kong
Objectives:	The primary objectives of this study are: • To assess the safety and tolerability of selonsertib (SEL), GS-0976, and GS-9674, administered alone or in combination, in subjects with bridging fibrosis or compensated cirrhosis due to NASH • To evaluate changes in liver fibrosis, as measured by the NASH Clinical Research Network (CRN) classification, without worsening of NASH (defined as any increase in hepatocellular ballooning or lobular inflammation)
Study Design:	This is a Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of SEL, GS-0976, GS-9674, and combinations in subjects with bridging fibrosis or compensated cirrhosis due to NASH. Subjects meeting the study's entry criteria will be randomly assigned in a 2:2:1:1:1:1:2 ratio to 1 of 7 treatment groups, with approximately 70 subjects in each combination treatment group and approximately 35 subjects in each single agent or placebo group, as shown in the figure below:



Randomized Study Phase

Randomization will be stratified by the presence or absence of diabetes mellitus, as determined by medical history or based on the Screening laboratory values if previously undiagnosed (hemoglobin A1c [HbA1c] $\geq$ 6.5% or fasting plasma glucose $\geq$ 126 mg/dL), and by the presence or absence of cirrhosis (F4) as determined by the central biopsy reader at Screening. Study drugs will be administered for a total of 48 weeks. Subjects who develop evidence of hepatic decompensation, including a Child-Pugh (CP) score $\geq$ 7 on at least two consecutive occasions at least two weeks apart, or undergo liver transplantation, must discontinue study drugs.

Number of Subjects Planned:	Approximately 350 subjects
Target Population:	Males and non-pregnant, non-lactating females between 18 – 80 years of age with bridging fibrosis or compensated cirrhosis due to NASH.
Duration of Study:	Participation can last up to 60 weeks, which includes an 8-week Screening period, a 48-week On-Treatment period, and a 4-week Follow-Up period.

Diagnosis and Main Eligibility Criteria:

Key Inclusion Criteria

1) Males and non-pregnant, non-lactating females between 18 - 80 years of age inclusive, based on the date of the Screening visit;

2) Bridging fibrosis or cirrhosis due to NASH as defined by one of the following; all subjects must not have documented weight loss > 5% between the date of the biopsy and Screening:

   a) NASH (defined as the presence of a steatosis grade ≥ 1, hepatocellular ballooning grade ≥ 1, and lobular inflammation grade ≥ 1, according to the nonalcoholic fatty liver disease [NAFLD] Activity Score [NAS]) and bridging fibrosis (F3) within 6 months of Screening, in the opinion of the central reader;

   b) Compensated cirrhosis (F4) due to NASH (defined as the presence of a steatosis grade ≥ 1, hepatocellular ballooning grade ≥ 1, and lobular inflammation grade ≥ 1, according to the NAS) within 12 months of Screening, in the opinion of the central reader;

   c) Compensated cirrhosis (F4) due to NASH with < 5% steatosis (defined as a steatosis grade of 0, hepatocellular ballooning grade ≥ 1, and lobular inflammation grade ≥ 1, according to the NAS) within 12 months of Screening, in the opinion of the central reader; and at least two of the following criteria for metabolic syndrome, modified from the National Cholesterol Education Program Adult Treatment Plan III {Grundy 2005} Guidelines at Screening:

      i. Fasting glucose ≥ 100 mg/dL or receiving drug treatment for elevated glucose;

      ii. Fasting HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women or receiving drug treatment for low HDL cholesterol;

      iii. Fasting triglycerides ≥ 150 mg/dL or receiving drug treatment for elevated triglycerides;

      iv. Waist circumference ≥ 102 cm for men or ≥ 88 cm for women or BMI ≥ 30 kg/m^2;

      v. Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or receiving drug treatment for hypertension;

d) In subjects who have never had a liver biopsy, liver stiffness by FibroScan® XL probe ≥ 14.0 kPa, Enhanced Liver Fibrosis (ELF™) Test score ≥ 9.8, and at least two of the criteria for metabolic syndrome modified from the NCEP ATP III Guidelines, at Screening. In subjects eligible based on this criterion, a liver biopsy must be performed during Screening and must be deemed evaluable for fibrosis stage and NAS by the central reader; however, the reported stage of fibrosis will not determine eligibility for the study;

3) Screening laboratory parameters, as determined by the central laboratory:

a) Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min, as calculated by the Cockcroft-Gault equation;

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

c) Hemoglobin ≥ 10.6 g/dL;

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

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

f) Platelet count ≥ 125,000/µL;

g) Serum triglyceride level ≤ 250 mg/dL;

h) Alanine aminotransferase (ALT) < 5 x ULN.

Key Exclusion Criteria

1) Prior history of decompensated liver disease including ascites, hepatic encephalopathy (HE), or variceal bleeding;

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

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

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

5) Chronic hepatitis C virus (HCV) infection (HCV antibody [Ab] and HCV ribonucleic acid [RNA] positive). Subjects cured of HCV infection less than 2 years prior to the Screening visit are not eligible;

6) Other causes of liver disease based on medical history and/or centralized review of liver histology, 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;
7) History of liver transplantation;
8) Current or prior history of hepatocellular carcinoma (HCC);
9) Any weight reduction surgery within 2 years prior to Screening or malabsorptive weight loss surgery (eg, Roux-en-Y or distal gastric bypass) at any time prior to Screening. Weight reduction surgery is disallowed during the study;
10) Intestinal resection that could result in malabsorption of study drug;
11) Weight loss > 10% within 6 months of Screening;
12) Human immunodeficiency virus (HIV) infection;
13) Unstable cardiovascular disease.

Study Procedures/ Frequency:

Screening assessments will include complete medical history, complete physical examination (PE) including assessment of ascites and HE, vital signs including weight, height, CCI [redacted], laboratory assessments including a serum pregnancy test (for females of childbearing potential), CCI [redacted], CCI [redacted] standard 12-lead electrocardiogram (ECG), CCI [redacted] and review of adverse events (AEs) and concomitant medications.

Eligible subjects will be randomized to one of seven treatment groups, with approximately 70 subjects in each combination treatment group and approximately 35 subjects in each single agent or placebo group:

Group A: SEL 18 mg, GS-0976 20 mg, and placebo to match (PTM) GS-9674 30 mg

Group B: SEL 18 mg, PTM GS-0976 20 mg, and GS-9674 30 mg

Group C: SEL 18 mg, PTM GS-0976 20 mg, and PTM GS-9674 30 mg

Group D: PTM SEL 18 mg, GS-0976 20 mg, and PTM GS-9674 30 mg

Group E: PTM SEL 18 mg, PTM GS-0976 20 mg, and GS-9674 30 mg

Group F: PTM SEL 18 mg, PTM GS-0976 20 mg, and PTM GS-9674 30 mg

Group G: PTM SEL 18 mg, GS-0976 20 mg, and GS-9674 30 mg

Prior to initial dosing, the following Day 1 assessments will be performed: symptom driven PE including assessment of ascites and HE, vital signs, body weight, CCI , laboratory assessments including a urine pregnancy test (for females of childbearing potential), CCI lifestyle questionnaire, lifestyle modification counseling, and review of AEs and concomitant medications. At selected sites, after eligibility is confirmed, CCI

After the randomization visit at Day 1, study visits will occur on Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

CCI

CCI

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

- Symptom driven PE at Weeks 1, 4, 8, 12, 16, 20, 28, 32, 36, 40, 44
- Complete PE at Weeks 24 and 48
- Vital signs including body weight at each visit
-
- 12-lead ECG at Week 48
- Chemistry, hematology, and coagulation at each visit
- HbA1c at Weeks 4, 12, 24, 36, and 48
- Insulin and lipids at Weeks 4, 12, 24, 36, and 48
-

[redacted]

- Urine pregnancy test (for females of childbearing potential) at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48

[redacted]

- Lifestyle questionnaire at each visit

[redacted]

- Liver biopsy at Week 48

[redacted]

All subjects will complete a Follow-Up visit 4 weeks after the date of last dose of study drugs. At this visit, subjects will have a symptom driven PE, vital signs, weight, CCI , 12-lead ECG, review of concomitant medications and AEs, CCI , and laboratory assessments including a urine pregnancy test (for females of childbearing potential).

Test Product and Dose	SEL 18 mg, GS-0976 20 mg, and GS-9674 30 mg oral tablets once daily, alone or in combination
Reference Therapy and Dose	PTM SEL 18 mg, PTM GS-0976 20 mg, and PTM GS-9674 30 mg oral tablets once daily

Treatment Groups and Mode of Administration:	• Treatment Group A: one SEL 18 mg tablet, one GS-0976 20 mg tablet, and one PTM GS-9674 30 mg tablet administered orally once daily with or without food • Treatment Group B: one SEL 18 mg tablet, one PTM GS-0976 20 mg tablet, one GS-9674 30 mg tablet administered orally once daily with or without food • Treatment Group C: one SEL 18 mg tablet, one PTM GS-0976 20 mg tablet, and one PTM GS-9674 30 mg tablet administered orally once daily with or without food • Treatment Group D: one PTM SEL 18 mg tablet, one GS-0976 20 mg tablet, and one PTM GS-9674 30 mg tablet administered orally once daily with or without food • Treatment Group E: one PTM SEL 18 mg tablet, one PTM GS-0976 20 mg tablet, and one GS-9674 30 mg tablet administered orally once daily with or without food • Treatment Group F: one PTM SEL 18 mg tablet, one PTM GS-0976 20 mg tablet, and one PTM GS-9674 30 mg tablet administered orally once daily with or without food • Treatment Group G: PTM SEL 18 mg, GS-0976 20 mg, and GS-9674 30 mg administered orally once daily with or without food
Criteria for Evaluation:	
Safety:	The safety of SEL, GS-0976, and GS-9674, alone or in combination, in subjects with bridging fibrosis or compensated cirrhosis due to NASH will be assessed during the study through the reporting of AEs, clinical laboratory tests, vital sign assessments, pruritus questionnaires, and concomitant medication usage. An external Data Monitoring Committee (DMC) that consists of two hepatologists and a statistician will review the progress of the study. The DMC will convene after 35 subjects (approximately 5 per treatment group) have completed the Week 4 assessments and approximately every 6 months thereafter to monitor for safety events.

Primary Endpoint: The primary endpoints are the safety and anti-fibrotic effects of SEL, GS-0976, and GS-9674, administered alone or in combination, in subjects with bridging fibrosis or compensated cirrhosis due to NASH.

Anti-fibrotic response will be evaluated by the proportion of subjects at Week 48 who achieve a ≥ 1-stage improvement in fibrosis (according to the NASH CRN classification) without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation).

CCI [redacted]

Statistical Methods

Safety Analysis: Safety analyses include summaries of extent of exposure, AEs, laboratory evaluations, and vital sign assessments.

Efficacy Analysis: **Primary Efficacy Endpoints Analysis:**

The point estimates and 95% confidence intervals for the proportion of subjects who achieve a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 48 will be calculated by treatment group.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Sample Size:	Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof of concept studies; however, with a sample size of approximately 70 subjects in each active combination treatment arm and approximately 35 in the placebo arm, the study has over 80% power to detect a difference in the proportion of subjects with a ≥ 1-stage improvement in fibrosis without worsening of NASH of 25% or more at Week 48 at a significance level of 0.05 (two-sided), assuming the proportion of subjects that meet the endpoint in the placebo arm is 7.2%.

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

α-SMA	alpha smooth muscle actin
µg	Microgram
ACC	acetyl-CoA carboxylase
AE	adverse event
AH	alcoholic hepatitis
AICD	automatic implantable cardioverter defibrillator
CCI [redacted]	[redacted]
aPTT	activated partial thromboplastin time
ASK1	apoptosis signal-regulating kinase 1
CCI [redacted]	[redacted]
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
AUC_{tau}	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
BAP	Biomarker Analysis Plan
BID	twice daily
BL	Baseline
BMI	body mass index
BUN	blood urea nitrogen
CAP	controlled attenuation parameter
CCR	Chemokine Receptor
CDHFD	choline-deficient high-fat diet
CFR	Code of Federal Regulations
CI	confidence interval
c-Jun	c-Jun protein
CK 18	cytokeratin 18
C_{last}	last observed quantifiable plasma/serum concentration of the drug
CL_{cr}	creatinine clearance
CLDQ-NAFLD	Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease
C_{max}	maximum observed plasma/serum concentration of drug
CMH	Cochran-Mantel-Haenszel
COL1A1	collagen type 1 alpha 1

CCI	[redacted]
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
DKD	Diabetic Kidney Disease
dL	Deciliter
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
EE	ethinyl estradiol
EFS	event-free survival
eg	Example
eGFR	estimated glomerular filtration rate
ELF™	Enhanced Liver Fibrosis
CCI	[redacted]
ESA	erythropoiesis-stimulating agents
EU	European Union
EudraCT	European clinical trial database
F2	Moderate Fibrosis
F3	Bridging Fibrosis
F4	Compensated Cirrhosis
CCI	[redacted]
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination

FGF19	fibroblast growth factor 19
FSH	follicle stimulating hormone
f_u	unbound fraction
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	gastrointestinal
GMR	geometric mean ratio
GSI	Gilead Sciences, Inc.
HA	hyaluronic acid
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
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IDE	investigational device exemption
IEC	independent ethics committee
IMP	Investigational Medicinal Product
CCI	[redacted]

IRB	institutional review board
IU	international units
IUD	intrauterine device
IV	Intravenous
IXRS	interactive mobile/web response system
JNK	c-Jun N-terminal kinase
kg	Kilogram
kPa	Kilopascal
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LEVO	Levonorgestrel
LLT	lower-level term
LOXL2	lysyl oxidase-like 2
LSM	least squares mean
M30	capsase-cleaved fragment of CK 18
M65	intact fragment of CK 18
MATE1	multidrug and toxin extrusion protein 1
MCV	mean corpuscular volume
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
mg	Milligram
MH	Mantel-Haenszel
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	millimeter of Mercury
MPQR2	multidrug resistance-associated protein
MQC	morphometric quantitative collagen
CCI	[redacted]
MRI	magnetic resonance imaging
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
NCEP ATP III	National Cholesterol Education Program Adult Treatment Plan III
NOAEL	no observed adverse event level

OATP	organic anion-transporting polypeptide
OCT1	organic cation transporter 1
OCT2	organic cation transporter 2
OL	Open-Label
OST-α	organic solute transporter alpha
OST-β	organic solute transporter beta
p38	mitogen-activated protein kinase p38
PAH	pulmonary arterial hypertension
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
p-p38	phospho-p38
PPAR	Peroxisome Proliferator-Activated Receptor
PSC	primary sclerosing cholangitis
PSR	picrosirius red
PT	prothrombin time / Preferred Term
PTM	placebo to match
PVE	Pharmacovigilance & Epidemiology
PVR	pulmonary vascular resistance
Q	Quarter
QD	once daily
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
rBA	relative bioavailability
RBC	red blood cell count
RIF	Rifampin
RNA	ribonucleic acid
ROC	receiver operating characteristic
ROS	reactive oxygen species
SADR	serious adverse drug reaction
SAE	serious adverse event
SAF	steatosis, activity, fibrosis
SAP	statistical analysis plan
SAS®	Statistical Analysis System

SD	standard deviation
SEL	Selonsertib
SF-36	Short Form 36 Health Survey
SIM	Simtuzumab
SOC	System Organ Class
SOP	standard operating procedure
SREBP-1c	sterol regulatory element binding protein-1c
SUSAR	Suspected Unexpected Serious Adverse Reaction
Sx	Symptoms of drug-related hepatotoxicity (eg, jaundice, right upper quadrant pain, nausea, vomiting, etc.)
$t_{½}$	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor beta
TIMP1	tissue inhibitor of metalloproteinase 1
T_{last}	last measured concentration
T_{max}	time (observed time point) of C_{max}
TPO	Thrombopoietin
UGT	UDP-glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
VAS	Visual Analog Scale
VORI	Voriconazole
WBC	white blood cell count
WPAI	Work Productivity and Activity Impairment Questionnaire

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 and metabolic syndrome that are leading to an increased incidence of NASH. Prevalence rates of hepatic steatosis or fatty liver, an entity that has been termed NAFLD, range from 6% to 37% worldwide {Ong 2007, Vernon 2011} with a recent pooled overall global prevalence of 25% reported {Younossi 2016}. NASH, the form of NAFLD associated with increased liver-related mortality, affects approximately 30% of all patients with NAFLD {Ong 2007, Williams 2011, Younossi 2016}. In the United States (US), it has been estimated that 2% to 5% of the population have NASH {Vernon 2011}, which is equivalent to approximately 16 million adults. Furthermore, as NASH is a manifestation of the metabolic syndrome, associated elevated cardiovascular risk factors (eg, atherosclerotic disease, cardiac arrhythmogenicity) likely coexist in patients with NASH {Dietrich 2014, Faramawi 2008, Voulgari 2010}. NASH represents a significant and growing unmet medical need for which there are no currently approved therapies.

NASH is primarily thought to occur as the result of the metabolic syndrome: the impact of obesity, hepatic insulin resistance, and dyslipidemia. Fatty liver, or simple steatosis, is not sufficient to cause liver injury; it is the presence of inflammation and hepatocellular injury on the background of steatosis that produces NASH and may result in the progression to cirrhosis and its complications including end-stage liver disease. 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) with progressive liver fibrosis {Dowman 2010, Koek 2011, Rolo 2012, Sumida 2013}. The major pathways in NASH disease progression include those involved in metabolic dysfunction in the hepatocyte, activation of hepatic stellate cells, and activation and recruitment of macrophages leading to hepatic inflammation and fibrosis. Advanced fibrosis and cirrhosis are characterized by extensive collagen deposition and remodeling of the extracellular matrix. Additionally, there is evidence which suggests that lipotoxic intermediates of fatty acids likely contribute to the etiology of NASH {Neuschwander-Tetri 2010}.

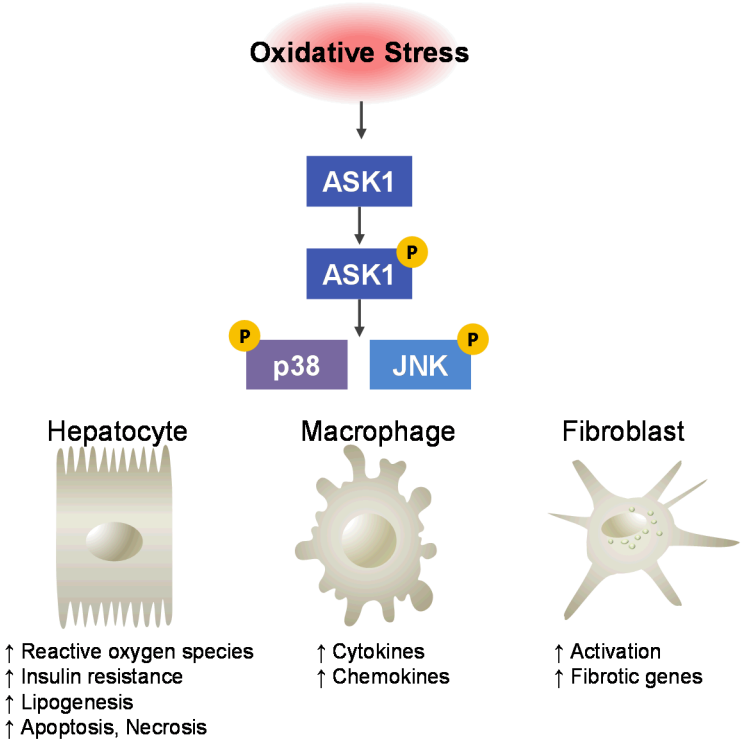
Over time, NASH may result in progressive liver fibrosis, ultimately resulting in cirrhosis. Advanced liver fibrosis (bridging fibrosis or cirrhosis) is associated with increased morbidity and mortality {Ekstedt 2014, Yeh 2014}. Cirrhosis increases the risk of developing HCC and other complications of end-stage liver disease, including jaundice, fluid retention (edema and ascites), portal hypertension and variceal hemorrhage, impaired coagulation, and HE. Decompensated liver disease, as defined by the development of one of the above complications, has a high mortality rate and the only 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. Selonsertib (SEL)

1.2.1. General Information for SEL

SEL is a potent and selective small molecule inhibitor of apoptosis signal-regulating kinase 1 (ASK1). ASK1 is a ubiquitously expressed serine/threonine kinase that is primarily activated by pathological oxidative stress {Makie 2007, Takeda 2008, Tobiume 2002}. ASK1 in turn phosphorylates and activates mitogen-activated protein kinase (p38) and c-Jun N-terminal kinases (JNK). p38 and JNK mediate metabolic, pro-inflammatory, and pro-fibrotic changes in the liver, which are central to disease progression in NASH. By inhibiting ASK1 signaling in patients with NASH, SEL is expected to halt progressive liver fibrosis and reverse existing fibrosis, thus preventing the development of cirrhosis-related complications. The mechanism of ASK1 signaling in NASH is presented graphically in Figure 1-1.

Figure 1-1. ASK1 Signaling in NASH



Increased ASK1 signaling is observed in liver biopsy specimens of patients with NASH, as demonstrated by increased levels of phosphorylated p38, which correlates with progression of fibrosis. ASK1 promotes a pathological cycle between oxidative stress, metabolic dysfunction, and hepatocellular damage and inflammation that ultimately promotes fibrosis and organ failure. These effects are the result of known roles of p38 and JNK signaling in hepatocytes, macrophages, hepatic stellate cells and fibroblasts, which have been demonstrated in preclinical studies.

Therefore, ASK1 signaling through p38 and JNK in hepatocytes, macrophages, and hepatic stellate cells promotes hepatocellular steatosis, apoptosis, necrosis, inflammation and fibrosis. SEL, by inhibiting oxidative stress-driven ASK1 signaling characteristic of NASH, is expected to halt progressive fibrosis and lead to regression of pre-existing fibrosis, thereby reducing progression to cirrhosis and its associated complications.

Please refer to the SEL Investigator's Brochure (IB) for additional details.

1.2.2. Nonclinical Pharmacology and Toxicology

SEL has been extensively evaluated in nonclinical toxicology studies. Findings attributed to SEL administration were primarily related to the cardiovascular system (mild decrease blood pressure and mild QT interval corrected for heart rate [QTc] prolongation), gastrointestinal (GI) tract (profuse diarrhea), kidney (tubular basophilia, eosinophilic droplets, and pigment), and embryofetal effects (visceral and/or skeletal malformations) occurred at exposures that were in excess of the targeted human exposure at 18 mg/day. Self-limiting diarrhea has been observed in subjects across the clinical studies. However, the low grade and self-limiting nature of the diarrhea suggests the diarrhea in the clinical studies is different from what was observed in monkeys.

Please refer to the SEL IB for additional details.

1.2.3. Clinical Trials of SEL

As of 28 November 2017, 15 Phase 1 and 2 clinical studies have been conducted/are ongoing in which 359 healthy subjects, 248 subjects with diabetic kidney disease (DKD), 113 subjects with pulmonary arterial hypertension (PAH), and 72 subjects with NASH have been dosed with SEL. In an ongoing Phase 2 study for severe alcoholic hepatitis (GS-US-416-2124), 50 additional subjects are planned for dosing. Phase 3 clinical studies have initiated in which an additional 640 NASH subjects with bridging fibrosis (Study GS-US-384-1943) and 640 NASH subjects with cirrhosis (Study GS-US-384-1944) are planned to be dosed.

Information on the completed and ongoing Phase 1 clinical studies and Phase 2 studies of DKD, PAH, and alcoholic hepatitis can be found in the IB.

1.2.3.1. Study GS-US-384-4266: A Phase 1 Drug Interaction Study Evaluating the Effect of Selonsertib on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Ethinyl Estradiol/Levonorgestrel

Study GS-US-384-4266 was a Phase 1, open-label study designed to evaluate the safety of SEL and the effect of SEL on the PK of a representative hormonal contraceptive, ethinyl estradiol/levonorgestrel (EE/LEVO), in healthy female subjects of childbearing potential. Subjects received a single oral dose of EE/LEVO (0.03/0.15 mg) alone and coadministered with SEL following 14 days of once daily dosing of SEL 18 mg.

1.2.3.1.1. Subject Disposition

A total of 16 subjects were enrolled. All 16 subjects (100%) completed the study.

1.2.3.1.2. Safety Results

No deaths, SAEs, Grade 3 or 4 AEs, AEs leading to discontinuation of study drug or study participation, or pregnancies were reported during the study. A total of 5 of 16 subjects (31.3%) experienced at least 1 AE during the study. All of the events were Grade 1 in severity, and no AE was experienced by more than 1 subject. Two subjects (12.5%) experienced AEs considered by the investigator to be related to study drug (menstruation irregularity [EE/LEVO] and headache [EE/LEVO + SEL]), both of which resolved prior to the end of the study. No clinically meaningful changes in laboratory values were noted, and there were no notable changes in vital sign measurements.

1.2.3.1.3. Pharmacokinetic Results

As shown in Table 1-1, similar systemic exposures (AUC_{inf}, AUC_{last}, and C_{max}) of LEVO and EE were observed following administration of LEVO/EE alone or in combination with SEL (18 mg once daily). All 90% CIs of the GLSM ratios for AUC_{inf}, AUC_{last}, and C_{max} were within the typical lack of PK alteration boundaries of 70% to 143%. No loss of contraceptive efficacy is expected upon administration of SEL with oral contraceptives like EE/LEVO.

Table 1-1. Pharmacokinetic Results from Study GS-US-384-4266 Evaluating DDE between SEL 18 mg QD and Representative Hormonal Contraceptive, Ethinyl Estradiol/Levonorgestrel

	Mean (% CV)		
Ethinyl Estradiol PK Parameter	**SEL + EE (Test) (N = 16)**	**EE (Reference) (N = 16)**	**%GLSM Ratio (90% CI) Test/Reference**
AUC_{inf} (h*ng/mL)	778.7 (29.2)	769.7 (45.6)	105.25 (94.72, 116.95)
AUC_{last} (h*ng/mL)	700.0 (31.2)	623.5 (35.9)	113.71 (106.20, 121.75)
C_{max} (ng/mL) (%)	88.8 (32.1)	74.2 (26.8)	117.76 (108.68,127.61)
	Mean (% CV)		
Levonorgestrel PK Parameter	**SEL + LEVO (Test) (N = 16)**	**LEVO (Reference) (N = 16)**	**%GLSM Ratio (90% CI) Test/Reference**
AUC_{inf}(h*ng/mL)	40.8 (45.7)	40.1 (42.9)	99.82 (89.49, 111.34)
AUC_{last} (h*ng/mL)	37.2 (43.7)	36.4 (40.1)	100.39 (90.16, 111.78)
C_{max} (ng/mL) (%)	3.7 (45.8)	3.3 (40.7)	112.74 (99.58, 127.64)

1.2.3.2. Study GS-US-384-1497: A Phase 2, Randomized, Open Label Study Evaluating the Safety, Tolerability, and Efficacy of Selonsertib alone or in Combination with Simtuzumab (SIM) in Subjects with Nonalcoholic Steatohepatitis (NASH) and Fibrosis (F2-F3)

This multicenter, randomized, open-label study evaluated the safety, tolerability, and efficacy of SEL (6 mg or 18 mg) alone or in combination with simtuzumab (SIM, a monoclonal antibody directed against lysyl oxidase-like 2 (LOXL2) evaluated for the treatment of NASH) versus SIM alone for 24 weeks in subjects with NASH and fibrosis stages F2 or F3.

1.2.3.2.1. Subject Disposition

A total of 72 subjects were randomized; 67 subjects (93.1%) completed study treatment. Of the 5 subjects who did not complete study treatment, 3 subjects discontinued due to AEs, 1 subject withdrew consent, and 1 subject was lost to follow-up.

1.2.3.2.2. Safety Results

Treatment with SEL (6 mg or 18 mg with or without SIM 125 mg) and SIM 125 mg was generally well tolerated. The 3 most common AEs were headache, nausea, and sinusitis. Most AEs were Grade 1 or Grade 2 in severity. Overall, 5 subjects had a Grade 3 AE; none of the Grade 3 AEs was reported in > 1 subject, and all but 1 were assessed as unrelated to study drug. No Grade 4 AEs were reported. Serious adverse events (SAEs) were reported for 5 subjects. There were no trends in SAE type or time of onset, and no SAE was reported in > 1 subject. Overall, 1 subject had an SAE that was assessed as related to study drug, and 3 subjects had AEs leading to premature discontinuation of study drug. No subjects died during the study.

The majority of subjects in each treatment group had at least 1 graded laboratory abnormality. The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. The most common Grade 3 laboratory abnormality was increased serum glucose. All of the subjects with Grade 3 increased glucose had graded elevations in glucose at baseline and at every study visit thereafter; all had a history of diabetes and were currently taking medication for diabetes. The only other Grade 3 laboratory abnormalities that were reported for ≥ 2 subjects were increased triglycerides (N = 3), increased ALT (N = 2), and increased aspartate aminotransferase (AST) (N = 2). Two subjects had Grade 4 increased gamma-glutamyl transferase (GGT). One of these subjects discontinued study drug due to Grade 1 increased hepatic enzymes. The other subject had elevated GGT throughout the study.

Across treatment groups, no clinically relevant changes from baseline to Week 24 were observed in measures of liver biochemistry, including alkaline phosphatase, ALT, AST, GGT, and total bilirubin. For all treatment groups, median values for ALT, AST, and GGT were in the high normal or above normal ranges at baseline and Week 24, although values for those parameters tended to decrease from baseline to Week 24.

No notable changes in vital sign measurements (temperature, pulse, systolic blood pressure, diastolic blood pressure, and respiration rate) or body weight were reported during the study. No trends in ECG findings suggestive of cardiac abnormalities were observed. No subject pregnancies were reported.

1.2.3.2.3. Summary of Efficacy Results

Treatment with SEL in GS-US-384-1497 resulted in histologic improvements in subjects with biopsy proven NASH and F2-F3 fibrosis. Although the small size of the study precluded formal statistical comparisons between treatment groups, numerically superior improvements were also consistently observed in the following endpoints in SEL treated compared with SIM-treated subjects:

- Subjects treated with SEL (18 or 6 mg) ± SIM 125 mg had a ≥ 1 stage decrease in NASH CRN fibrosis stage from baseline in 43.3 % and 29.6 % of subjects, respectively, compared with 20.0% of subjects treated with SIM 125 mg alone.

- Subjects treated with SEL (18 or 6 mg) ± SIM 125 mg were less likely to have worsening of fibrosis (6.7% and 14.8%, respectively) or progression to cirrhosis (3.3% and 7.4%, respectively) compared with subjects treated with SIM 125 mg alone (40.0% with worsening of fibrosis and 20.0% with progression to cirrhosis).

- Consistent with fibrosis stage improvement, subjects treated with SEL (18 or 6 mg) ± SIM 125 mg had reductions in hepatic collagen content as measured by morphometric quantitative collagen (MQC) (−8.7% and −8.2%, respectively) versus an increase of 2.1% in subjects treated with SIM 125 mg alone.

- Greater reductions in cytokeratin 18 (CK 18) capsase-cleaved fragment of CK 18 (M30) and intact fragment of CK 18 (M65) fractions in subjects treated with SEL (18 or 6 mg) ± SIM 125 mg versus SIM 125 mg alone, indicate reduced rates of hepatocellular apoptosis and necrosis, and are consistent with improvements in fibrosis stage and liver biochemistry tests. The dose-dependent reductions in CK18 M30 and M65 fractions also support the mechanism of action of SEL.

Across all treatment groups, no clinically significant worsening in metabolic or cardiovascular risk factors from baseline and no significant change in weight were observed at Week 24.

Collectively, these data support that SEL treatment results in fibrosis regression, improvements in liver biochemistry, and reductions in hepatic fat, inflammation, and apoptosis in subjects with NASH and moderate to severe liver fibrosis.

For further information on SEL in Phase 2 NASH clinical trials, refer to the SEL IB.

1.3. GS-0976

1.3.1. General Information for GS-0976

GS-0976 is a small molecule allosteric inhibitor of acetyl-CoA carboxylase (ACC). ACC catalyzes the conversion of acetyl-CoA to malonyl-CoA, the rate-limiting and first committed step in fatty acid synthesis. GS-0976 is being developed for the treatment of NASH, a metabolic disorder characterized by dysregulated fatty acid metabolism.

Dysregulated fatty acid metabolism occurs via elevated fatty acid synthesis, impaired fatty acid oxidation, or both. Therefore, inhibition of fatty acid synthesis and/or stimulation of fatty acid oxidation have the potential to favorably affect several metabolic diseases and sequelae. ACC is a critical enzyme in both fatty acid synthesis and fatty acid oxidation. Due to this unique position in intermediary metabolism {Harwood 2005, Tong 2006}, pharmacologic inhibition of ACC presents an attractive strategy for limiting fatty acid synthesis in lipogenic tissues while simultaneously stimulating fatty acid oxidation in oxidative tissues {Harwood 2005}.

Please refer to the GS-0976 IB for additional details.

1.3.2. Nonclinical Pharmacology and Toxicology

GS-0976 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 GS-0976 can reduce the *de novo* lipogenesis (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. In total, these studies confirm the potential for GS-0976 to impact important metabolic endpoints associated with NASH.

The nonclinical toxicologic profile of GS-0976 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.

GS-0976 was well tolerated for 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 did, whereas they did at 3-times higher mean GS-0976 exposure. In the females, the lowest exposure where lens degeneration was observed was 5-times higher than the clinical exposure at 20 mg GS-0976.

In contrast, in the 13-week mouse study, there were no eye findings that were attributed to GS-0976 at exposures approximately 8-fold above the clinical exposure at 20 mg. While the relevance to humans of the lens degeneration observed in the mouse is currently unknown, the lack of eye findings attributable to GS-0976 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 GS-0976 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.

GS-0976 was not genotoxic and there was no embryo-fetal developmental toxicity at exposures approximately 50-times the clinical exposure. GS-0976 was considered non-corrosive and does not require classification as an eye irritant.

Based on the systemic concentrations of GS-0976 measured in the repeat-dose toxicity studies in mice, rat, and dog at the projected clinically efficacious area under the plasma/serum concentration versus time curve (AUC) (88 ng•h/mL), the margins of exposure at the no observed AE levels (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 GS-0976.

Please refer to the GS-0976 IB for additional details.

1.3.3. Clinical Trials of GS-0976

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 GS-0976 IB.

1.3.3.1. Study GS-US-426-4074: A Phase 1 Study to Evaluate Transporter and Cytochrome (CYP) 450-Mediated Drug-Drug Interactions Between GS-0976 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 GS-0976 (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 GS-0976, as assessed by changes in fractional DNL, will also be evaluated.

1.3.3.1.1. 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.

1.3.3.1.2. 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.

1.3.3.1.3. 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 GS-0976 20 mg (N=28). Single doses of CsA and RIF significantly increased GS-0976 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 GS-0976 is a sensitive substrate of hepatic OATP with intestinal P-gp playing a minimal role in GS-0976 absorption as seen by a smaller increase in GS-0976 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 GS-0976 20 mg (N=14). Co-administration of GS-0976 with PBC resulted in a moderate increase in GS-0976 exposure (61%) indicating UGTs are involved in the metabolism of GS-0976. 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 GS-0976 with VORI increased GS-0976 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 GS-0976 50 mg once daily on a sensitive CYP3A4 probe substrate (midazolam [MDZ] 2 mg: MDZ; N=12). Neither single dose nor multiple doses of GS-0976 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 GS-0976 is not an inhibitor or inducer of CYP3A4.

Cohort 6: Impact of single and multiple doses of GS-0976 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 GS-0976 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 GS-0976 slightly increased EE exposure (AUC_{inf} increased ~34%) with no effect on DRSP exposure indicating GS-0976

does not induce enzymes/transporters involved in the clearance of DRSP or EE. No loss of contraceptive efficacy is expected upon administration of GS-0976 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 GS-0976 (20 mg or 50 mg)

Inhibitor/Inducer Drug	GS-0976 %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 GS-0976 %GMR (90% CIs)		**MDZ + MD GS-0976 %GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
GS-0976 (50 mg)	111 (99.8, 123)	102 (91.6, 115)	102 (91.4, 113)	106 (94.9, 119)
	DRSP + SD GS-0976 %GMR (90% CIs)		**DRSP + MD GS-0976 %GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
GS-0976 (50 mg)	96.4 (86.5, 107)	103 (91.5, 116)	105 (94.0, 117)	116 (102, 131)
	EE + SD GS-0976 %GMR (90% CIs)		**EE + MD GS-0976 %GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
GS-0976 (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

1.3.3.2. Study GS-US-426-3988: A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of GS-0976 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 GS-0976 in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment (CP class A, B, or C, respectively). Up to 60 subjects are planned for enrollment in 1 of 3 hepatic impairment cohorts: Cohort 1 (mild hepatic impairment), Cohort 2 (moderate hepatic impairment), and Cohort 3 (severe 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 GS-0976 20 mg in a fasted state on Day 1. Subjects in Cohort 3 will receive a single oral dose of GS-0976 5 mg in a fasted state on Day 1.

1.3.3.2.1. Subject Disposition and Demographics

As of 17 November 2017, a total of 36 subjects were dosed; 34 subjects had completed study treatment. No subjects prematurely discontinued study treatment. No subjects withdrew consent, and no subjects were lost to follow-up.

1.3.3.2.2. 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 were 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.

1.3.3.2.3. Preliminary PK Results

Preliminary PK results from Cohorts 1 and 2 are presented below and in Table 1-3:

- Cohort 1 (Mild Hepatic Impairment; CP A): GS-0976 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. GS-0976 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 GS-0976. 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): GS-0976 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 GS-0976 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 GS-0976 metabolism (ie, UGTs and CYP3A4). At a dose of 20 mg QD, GS-0976 plasma exposures in subjects with moderate hepatic impairment are $\geq$ 5-fold and $\geq$ 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 GS-0976 and GS-834773 PK Parameters Following a Single Dose of GS-0976 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)	Mild Hepatic Impairment (N=10)	%GMR (90% CI)
1	GS-0976	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	GS-0976	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 GS-0976, dose adjustments are not considered necessary in subjects with mild hepatic impairment.

1.3.3.3. A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-0976 in Subjects with Nonalcoholic Steatohepatitis (GS-US-426-3989)

Study GS-US-426-3989 is a completed Phase 2, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and efficacy of GS-0976 in subjects with NASH. To be eligible to participate, subjects were required to have a clinical diagnosis of NAFLD with imaging or a liver biopsy documenting fatty liver within 2 years prior to Screening, MRI-PDFF with ≥ 8% steatosis, and MRE with liver stiffness ≥ 2.5 kPa at Screening, or a historical liver biopsy within 12 months of Screening consistent with NASH and no documented weight loss > 5% between the date of the liver biopsy and Screening.

The primary endpoint was the safety of GS-0976. Exploratory efficacy endpoints included changes from baseline in steatosis as measured by MRI-PDFF, liver stiffness as measured by both MRE and FibroScan®, noninvasive markers of fibrosis including ELF™ Test, markers of liver injury and function (ALT, AST, bilirubin, GGT and alkaline phosphatase [ALP]), homeostatic assessment of insulin resistance (HOMA-IR), serum lipid profiles, and HbA1c levels.

1.3.3.3.1. Subject Disposition

A total of 127 subjects were randomized (50 in the GS-0976 20 mg group, 51 in the GS-0976 5 mg group, and 26 in the placebo group). Of the 127 randomized subjects, 126 received at least 1 dose of study drug (49 in the GS-0976 20 mg group, 51 in the GS-0976 5 mg group, and 26 in the placebo group).

A total of 121 subjects (96.0%) completed study drug treatment: 48 (98.0%) in the GS-0976 20 mg group, 47 (92.2%) in the GS-0976 5 mg group, and 26 (100.0%) in the placebo group. A total of 118 subjects (93.7%) completed the study: 46 (93.9%) in the GS-0976 20 mg group, 46 (90.2%) in the GS-0976 5 mg group, and 26 (100.0%) in the placebo group.

1.3.3.3.2. Safety Results

Treatment with GS-0976 20 or 5 mg was generally well tolerated. The most common AEs in each treatment group were nausea, abdominal pain, and diarrhea (GS-0976 20 mg); diarrhea, headache, and hypertriglyceridemia (GS-0976 5 mg); and fatigue, sinusitis, nausea, chest discomfort, constipation, and dyspnea (placebo). Most AEs were Grade 1 or 2 in severity. Overall, 5 subjects had a Grade 3 AE; none of the Grade 3 AEs was reported in > 1 subject, and all but 1 were considered unrelated to study drug. One Grade 4 AE, which was not considered treatment-related, was reported. SAEs were reported for 4 subjects and included transient ischemic attack, sepsis, pyrexia, abdominal pain, HE, and diverticulitis. There were no trends in SAE type or time of onset, no SAE was reported in > 1 subject, and all SAEs were considered unrelated to study drug. Two subjects had AEs leading to premature discontinuation of study drug; for 1 of these subjects, the AEs leading to study drug discontinuation (pruritus, rash papular, and night sweats) were considered treatment-related. No deaths occurred during the study.

The majority of subjects had at least 1 graded laboratory abnormality. The majority of laboratory abnormalities were Grade 1 or 2 in severity. Overall, the most common Grade 3 or 4 laboratory abnormalities in subjects receiving GS-0976 were elevated triglycerides (hypertriglyceridemia; 16.0%, 16 of 100 subjects) and elevated glucose (hyperglycemia; 10.0%, 10 of 100 subjects), which only occurred in subjects who received GS-0976. The majority of subjects with Grade 3 or 4 hypertriglyceridemia had a medical history of hyperlipidemia or hypertriglyceridemia, and had graded elevations in triglycerides at baseline. Grade 3 or 4 hyperglycemia was reported for 10 subjects, all of whom had a medical history of diabetes and were taking medication for diabetes, and 7 of whom had HbA1c > 9.0% at baseline.

A total of 8 subjects met criteria for Drug Induced Liver Injury (DILI) monitoring, 4 of whom experienced liver-related laboratory abnormalities that were at least Grade 3 in severity, including Grade 3 elevated ALT, Grade 3 elevated AST, and/or Grade 3 elevated GGT. All 4 subjects had graded abnormalities in the respective analytes at baseline. No AEs associated with the liver-related laboratory abnormalities were reported for any of the 4 subjects, and all 4 subjects completed treatment with study drug.

No notable changes in vital sign measurements or body weight were reported during the study. No clinically significant ECG abnormalities were reported. No subject pregnancies were reported.

1.3.3.3.3. Efficacy Results

Larger median (quarter (Q) 1, Q3) decreases from baseline in liver steatosis as measured by MRI-PDFF (in %) were observed in the GS-0976 groups compared with the placebo group, with the largest decrease in the GS-0976 20 mg group: −4.99 (−8.15, −0.78) in the GS-0976 20 mg group, −2.22 (−4.33, 0.07) in the GS-0976 5 mg group, and −0.94 (−1.94, 1.41) in the placebo group. These decreases corresponded with median (Q1, Q3) percent decreases of −28.9% (−47.7%, −11.9%) in the GS-0976 20 mg group, −13.0% (−28.5%, 0.6%) in the GS-0976 5 mg group, and −8.4% (−18.2%, 9.6%) in the placebo group. The difference (GS-0976 vs placebo) in least squares mean (LSM) change from baseline in MRI-PDFF at Week 12 was statistically significant for the GS-0976 20 mg group (−3.42% [95% CI: −5.73, −1.11; p = 0.004]).

Larger proportions of subjects in both GS-0976 groups had at least 30% reduction in MRI-PDFF at Week 12 compared with the placebo group: 47.8% (22 of 46 subjects) in the GS-0976 20 mg group, 23.4% (11 of 47 subjects) in the GS-0976 5 mg group, and 15.4% (4 of 26 subjects) in the placebo group. The difference in proportions between the GS-0976 20 mg and placebo groups was statistically significant (31.8% [95% CI: 10.5%, 53.2%; p = 0.004]).

In contrast, no statistically significant differences between the GS-0976 groups and the placebo group were observed for the MRE endpoints. The proportions of subjects with at least 15% reduction in MRE at Week 12 were 32.6% (15 of 46 subjects) in the GS-0976 20 mg group, 40.4% (19 of 47 subjects) in the GS-0976 5 mg group, and 34.6% (9 of 26 subjects) in the placebo group.

At Week 12, larger median (Q1, Q3) percent decreases from baseline in liver stiffness by FibroScan® were observed in both GS-0976 groups compared with the placebo group: −11.1% (−34.1%, 13.5%) in the GS-0976 20 mg group, −8.4% (−29.7%, 8.8%) in the GS-0976 5 mg group, and −3.1% (−21.6%, 22.3%) in the placebo group.

Slightly smaller median percent decreases from baseline in ELF™ Test score at Week 12 were observed in the GS-0976 groups compared with the placebo group: −0.8% (−4.5%, 2.1%) in the GS-0976 20 mg group, −0.9% (−5.0%, 3.0%) in the GS-0976 5 mg group, and −1.7% (−3.2%, 0.7%) in the placebo group. At Week 12, median (Q1, Q3) percent changes from baseline in each component of ELF™ Test score were as follows:

- Hyaluronic acid (HA): −6.9% (−22.2%, 35.0%) in the GS-0976 20 mg group, −0.7% (−29.0%, 30.3%) in the GS-0976 5 mg group, and −15.3% (−25.4%, 20.9%) in the placebo group
- Tissue inhibitor of metalloproteinase 1 (TIMP1): −7.9% (−17.2%, 0.1%) in the GS-0976 20 mg group, −2.9% (−13.9%, 5.8%) in the GS-0976 5 mg group, and 1.5% (−9.0%, 10.6%) in the placebo group
- Procollagen III amino terminal peptide (PIIINP): −13.9% (−23.6%, 9.4%) in the GS-0976 20 mg group, −7.0% (−15.3%, 10.9%) in the GS-0976 5 mg group, and −0.5% (−7.9%, 4.3%) in the placebo group.

Larger median (Q1, Q3) percent decreases from baseline in ALT at Week 12 were observed in both GS-0976 groups compared with the placebo group: −20.5% (−41.1%, 8.0%) in the GS-0976 20 mg group, −9.8% (−26.2%, 5.1%) in the GS-0976 5 mg group, and −6.7% (−17.6%, 2.7%) in the placebo group. Larger median (Q1, Q3) percent decreases from baseline in AST were also observed in both GS-0976 groups compared with the placebo group: −5.6% (−38.6%, 19.4%) in the GS-0976 20 mg group, −9.3% (−18.2%, 6.3%) in the GS-0976 5 mg group, and −3.5% (−23.7%, 10.8%) in the placebo group. Changes from baseline in other liver biochemistry parameters (ALP, GGT, and total bilirubin) were not clinically relevant.

At Week 12, median (Q1, Q3) percent increases from baseline in triglycerides were observed in both GS-0976 groups compared with a decrease in the placebo group: 10.8% (−4.2%, 48.0%) in the GS-0976 20 mg group, 12.9% (−9.9%, 57.2%) in the GS-0976 5 mg group, and −4.3% (−18.3%, 16.5%) in the placebo group. No notable changes from baseline to Week 12 in other lipid parameters, HbA1c, or glucose were observed in any treatment group.

Please refer to the GS-0976 IB for additional details.

1.4. GS-9674

1.4.1. General Information for GS-9674

GS-9674 is a potent agonist of 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.

Please refer to the GS-9674 IB for additional details, including:

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

1.4.2. Nonclinical Pharmacology and Toxicology

In vivo pharmacology studies have demonstrated that GS-9674 preferentially activates intestinal FXR and reduces liver fibrosis. In cynomolgus monkeys, there was an increase in circulating FGF19 levels after oral dosing of GS-9674 but not after intravenous (IV) dosing despite greater exposure to GS-9674 after IV dosing. These data suggest that intestinal FXR agonism by GS-9674 causes FGF19 production, whereas low systemic free drug concentrations limit effects following IV administration of GS-9674. In addition, the oral administration of GS-9674 to monkeys directly activated intestinal FXR, as measured by the expression of FXR-target genes in the ileum (FGF19, organic solute transporter alpha (OSTα), organic solute transporter beta (OSTβ) mRNA). In a mouse model of NASH induced by a diet enriched in fat, cholesterol and sugar, GS-9674 reduced hepatic steatosis and normalized bile acid levels in plasma. In a CDHFD/sodium nitrite ($NaNO_2$) rat model of liver fibrosis that utilizes "2 hits" to mimic the metabolic and oxidative stress components of NASH in humans, GS-9674 dose dependently reduced both biochemical and histological measures of liver fibrosis. Overall, the results from these pharmacology studies demonstrate that GS-9674 is a potent and selective agonist of intestinal FXR with the potential to benefit NASH patients by inducing FGF19 production.

The nonclinical toxicity profile of GS-9674 has been assessed in mice and cynomolgus monkeys administered GS-9674 orally for up to 26 and 39 weeks, respectively. Findings attributed to GS-9674 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 GS-9674. These findings were minimal to mild, non-adverse, and reversible after discontinuation of treatment. The 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 GS-9674 QD with food.

Please refer to the GS-9674 IB for additional details.

1.4.3. Clinical Trials of GS-9674

As of 1 November 2017, 6 Phase 1 clinical studies have been completed or are ongoing and 4 Phase 2 studies in subjects with NASH, PBC, and PSC are ongoing.

Information about completed and ongoing clinical studies can be found in the current GS-9674 IB.

1.4.3.1. Study GS-US-454-4315: A Phase 1 Study to Evaluate the Relative Bioavailability and Food Effect of Single Agent Tablets and Fixed Dose Combinations of GS-9674, GS-0976, and/or Selonsertib in Healthy Subjects Study

GS-US-454-4315 is an ongoing Phase 1 open-label, multiple cohort, crossover study to assess the relative bioavailability (rBA) (Part A) of fixed dose combination (FDC) tablets of GS-9674, GS-0976, and/or SEL compared to single agent tablets administered in combination in healthy subjects. Food effect was evaluated in Part A on SEL and GS-0976 administered as an FDC tablet (SEL/GS-0976) and GS-9674 and GS-0976 each administered as single agent tablets. Supratherapeutic exposure (Part B) of GS-9674 was also assessed. Approximately 90 subjects were enrolled into 4 pre-specified cohorts: Cohorts 1 to 3 in Part A and Cohort 4 in Part B.

1.4.3.1.1. Subject Disposition

Of the 90 enrolled subjects, all received at least 1 dose of study drug. A total of 89 of 90 subjects (98.9%) completed treatment with study drug and completed the study. One subject in Cohort 2 prematurely discontinued the study due to an AE of urticaria.

1.4.3.1.2. Preliminary Safety Results

Administration of GS-9674, SEL, and GS-0976 was generally well tolerated in healthy subjects. No deaths, SAEs, Grade 4 AEs, or pregnancies were reported during this study.

One subject experienced a Grade 2 AE of acute urticaria on Day 13 following treatment with SEL + GS-0976 (single agent tablets) on Day 1 and SEL/GS-0976 (FDC) on Day 9. This led to the discontinuation of study participation, and this event was considered related to study drug by the investigator.

A total of 12 of 90 subjects (13.3%) experienced at least 1 AE, and the most commonly reported AEs overall were lower abdominal pain (4 subjects, 4.4%) and headache (2 subjects, 2.2%). No trends in the overall frequency or type of AEs were observed between the FDC tablets and coadministration of their respective single agent tablets, between administration of therapy in the fed versus fasted state, and between supratherapeutic dosing of GS-9674 at 100 mg TID, with 1.0 hr separation versus 0.5 hr separation.

Overall, 6 of 90 subjects (6.7%) experienced an AE that was considered to be related to study drug by the investigator. The most commonly reported study drug-related AEs overall were lower abdominal pain (4 subjects, 4.4%) and headache (2 subjects, 2.2%). With the exception of the Grade 2 AE of acute urticaria, all other study drug-related AEs were Grade 1 in severity and did not require discontinuation from the study.

A total of 47 of 90 subjects (52.2%) experienced a graded laboratory abnormality. The majority of laboratory abnormalities were Grade 1 or 2 in severity, and no Grade 4 laboratory abnormalities were observed. Eight of the 90 subjects (6.5%) had a Grade 3 laboratory abnormality: increased LDL cholesterol (2 subjects) and occult blood in urine (6 subjects). Both subjects who had a Grade 3 increased LDL cholesterol had Grade 1 or 2 increased LDL

cholesterol at baseline and at all other on-study measurements. The Grade 3 laboratory abnormalities of occult blood in urine were not associated with any AEs, all occurred in females of childbearing potential, and were deemed by the investigator to be due to menses.

No notable changes in vital sign measurements or clinically significant ECG abnormalities were observed during the study.

1.4.3.1.3. Preliminary PK Results

Preliminary results on the effect of food on GS-9674 PK are presented below and in Table 1-4.

The effect of food on GS-9674 single agent tablets has previously been evaluated using a moderate fat meal, which demonstrated a 33% to 35% decrease in GS-9674 exposure (AUC). The changes in the primary PK parameters for GS-9674 and its metabolite, GS-716070, following a single dose administration of GS-9674 single-agent tablet under fed (light meal or high-fat meal) versus fasting conditions were evaluated in this study and the preliminary results are summarized in the table below. Both SEL and GS-0976 have previously been shown to not significantly affect GS-9674 PK when administered as single agent tablets. Thus, comparison of GS-9674 PK following co-administration of GS-9674 with SEL or GS-0976 and a high-fat meal (Treatments A and G, respectively) to administration of GS-9674 alone in the fasted state (Treatment C) was considered acceptable to evaluate the effect of food on GS-9674 single agent tablets. Administration of GS-9674 alone (Treatment I) with a light meal decreased both AUC_{inf} and C_{max} of GS-9674 (63% and 68%, respectively) as compared to administration of GS-9674 alone (Treatment C) under fasted conditions. Administration of GS-9674 with a high-fat meal increased GS-9674 exposure (AUC_{inf}) 37% to 42% as compared to fasted conditions with minimal changes in C_{max} (-7% to 1%). Changes in PK of the metabolite, GS-716070, were similar to those of parent.

Table 1-4. GS-US-454-4315: Summary of Changes in Primary PK Parameters for GS-9674 and GS-716070 Following Administration of GS-9674 Single Agent Tablets with a Light Meal or High-Fat Meal as Compared to Fasted State

	Light Meal vs Fasted (Treatment I vs C)	High-Fat Meal vs Fasted (Treatment A vs C)	High-Fat Meal vs Fasted (Treatment G vs C)
GS-9674			
AUC_{inf}	↓ 63%	↑ 42%	↑ 37%
AUC_{last}	↓ 63%	↑ 44%	↑ 39%
C_{max}	↓ 68%	↑ 1%[a]	↓ 7%
GS-716070			
AUC_{inf}	↓ 65%	↑ 34%	↑ 23%
AUC_{last}	↓ 66%	↑ 37%	↑ 24%
C_{max}	↓ 68%	↑ 1%[a]	↓ 11%

The 90% CIs of the %GLSM ratios for test versus reference treatments were within (↔), extended above (↑), or extended below (↓) the predefined lack of PK alteration boundaries of 70% to 143%. Percentages indicate the increase or decrease in the geometric mean for the respective PK parameter for test treatment relative to reference treatment.

a The 90% CIs of the %GLSM ratio for test versus reference treatment extended both above and below the predefined lack of PK alteration boundaries of 70% to 143%.

1.4.3.2. Study GS-US-402-3885: A Phase 1 Open-Label, Parallel-Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics and Pharmacodynamics of GS-9674 in Subjects with Normal and Impaired Hepatic Function

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 GS-9674 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 will receive a single oral dose of GS-9674 30 mg in the fed state on Day 1 with PD collected on Day -1 and Day 1.

1.4.3.2.1. 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 AE, withdrew consent, or were lost to follow-up.

1.4.3.2.2. Preliminary Safety Results

Overall, 8.8% of subjects had a treatment-emergent adverse event (TEAE) of Grade 1 or 2. There was 1 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 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, 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.

1.4.3.2.3. Preliminary PK Results

Preliminary PK results are presented below and in Table 1-5:

- Cohort 1 (mild hepatic impairment; CP A): GS-9674 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). Both analytes had minor changes in plasma protein binding (unbound fraction [f_u] increased ~30%). GS-9674 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 GS-9674. At a dose of 30 mg 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): GS-9674 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}. Plasma unbound fraction (f_u) of GS-9674 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 metabolite, respectively.

Table 1-5. GS-US-402-3885: Preliminary GS-9674 and GS-716070 PK Parameters Following a Single Dose of GS-9674 30 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	GS-9674	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)
2	GS-9674	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)

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 GS-9674. Changes in FGF19 and C4 following a single dose of GS-9674 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 $AUC_{2\text{-}12hr}$ for FGF19 (1.1 and 1.1, respectively) and for C_{min} and $AUC_{2\text{-}12hr}$ 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 GS-9674, dose adjustments are not considered necessary in subjects with mild hepatic impairment.

1.4.3.3. Study GS-US-402-1852: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Nonalcoholic Steatohepatitis (NASH)

GS-US-402-1852 is an ongoing Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and efficacy of GS-9674 in subjects with NASH and fibrosis. Eligibility of potential subjects is based upon a clinical diagnosis of NAFLD, a historical liver biopsy within the previous 12 months consistent with NASH and non-cirrhotic fibrosis, or a MRI-PDFF with ≥ 8% steatosis and MRE with liver stiffness ≥ 2.5 kPa.

1.4.3.3.1. Subject Disposition

As of September 2017, study GS-US-402-1852 randomized 140 subjects, with 128 active, 8 completed, and 4 early terminated from the study. The number of subjects with ≥ 12 weeks of study drug exposure was 112/140 (80%) and 17/140 (12.1%) had completed 24 weeks of study drug treatment.

1.4.3.3.2. Preliminary Safety Data

As of September 2017, four subjects have early terminated from the study due to AEs. One patient developed right upper quadrant pain two weeks into the study and was subsequently found to have a duodenal lymphoma. Three patients discontinued the study due to pruritus with resolution of symptoms after study drug discontinuation.

1.5. Combination Studies of SEL, GS-0976, and GS-9674

1.5.1. Nonclinical Pharmacology, Pharmacokinetics, Drug Metabolism, and Toxicology

Given that ASK1, FXR, and ACC mediate distinct biological pathways and cellular mechanisms that contribute to NASH pathophysiology, it is hypothesized that combinations of SEL, GS-9674, and GS-0976 will provide greater benefit to reduce or reverse NASH progression.

In support of this hypothesis, pairwise combinations of an ASK1 inhibitor, an FXR agonist, and an ACC inhibitor were well tolerated and caused a greater reduction in fibrosis compared to the respective single agents in a rat choline-deficient, high-fat diet (CDHFD) model of fibrosis. Rats were fed a CDHFD for 6 weeks to induce severe lipotoxicity in the liver and moderate fibrosis. The animals were then maintained on the CDHFD for another 6 weeks while being treated therapeutically with a vehicle control, ASK1 inhibitor, FXR agonist, ACC inhibitor or pairwise combinations of each drug. Fibrosis was assessed histologically by staining extracellular matrix with picrosirius red (PSR). Additionally, the number of activated hepatic stellate cells was quantified by staining liver sections with antibodies against α–SMA and desmin. Quantitative morphometry was performed to determine the percent positive area for each marker. Treatment with the ASK1 inhibitor monotherapy or FXR agonist monotherapy led to small and nonsignificant reductions in PSR area whereas the ACC inhibitor monotherapy led to a significant reduction in PSR area of about 50% relative to vehicle control animals. The FXR and

ASK1 combination significantly decreased PSR area by 69% relative to vehicle control animals, which was significantly greater efficacy than that for each respective single agent. Combinations of the ACC inhibitor with either the ASK1 inhibitor or the FXR agonist trended towards greater reduction in PSR % area than the ACC inhibitor alone, each reaching 60% reduction. All pairwise combinations significantly reduced alpha smooth muscle actin (α-SMA) and desmin area to a greater extent than the single agents alone. In addition, all pairwise combinations led to greater reductions in plasma markers of fibrosis TIMP1 and PIIINP compared to each respective single agent. These data demonstrate that pairwise combinations of each of the agents increased anti-fibrotic efficacy assessed by multiple different markers. Therefore, combinations of SEL, GS-9674 and GS-0976 have the potential to induce a greater magnitude of fibrosis reversal in subjects with NASH.

Pairwise combinations of an ASK1 inhibitor, an FXR agonist, and an ACC inhibitor also increased efficacy relative to the respective monotherapies in a mouse model of NASH. Mice were fed a diet high in fat, sugar and cholesterol for five months to induce hepatic steatosis and expression of fibrogenesis-related genes as well as elevated plasma ALT levels. The animals were then treated for 28 days with a vehicle control, ASK1 inhibitor, FXR agonist, ACC inhibitor or pairwise combinations of each drug. All combinations resulted in significantly greater reductions in hepatic steatosis, hepatic cholesterol and triglyceride levels, and plasma ALT levels compared to animals treated with the respective monotherapies. In addition, the combination therapies caused a greater reduction in mRNA levels of genes associated with fibrogenesis collagen type 1 alpha 1 (COL1A1), TIMP1, and platelet-derived growth factor beta (PDGF-β).

Pharmacodynamic analysis for ASK1, FXR, and ACC signaling confirmed that these targets regulate independent pathways that contribute to NASH pathogenesis. Treatment of mice with an ASK1 inhibitor did not agonize the FXR pathway or inhibit the ACC pathway. Similarly, treatment of mice with an FXR agonist did not impinge on the ASK1 or ACC pathways and the ACC inhibitor did not agonize the FXR pathway or inhibit the ASK1 pathway. Therefore, each agent is expected to cause a therapeutic benefit independent of the other monotherapies.

In a 13-week repeat-dose combination toxicity mouse study, GS-0976 and GS-9674, when administered separately or in combination, resulted in no adverse findings. The NOAEL for the combination groups was considered to be 20/3 mg/kg/day GS-9674/GS-0976, the highest dose group tested. Exposures of GS-0976 and GS-9674 in the highest combination mouse group were approximately 6-fold higher than the clinical exposure of each compound.

GS-0976 was also administered in combination with SEL to rats for 13 consecutive weeks. Microscopic findings of hyperkeratosis and hyperplasia, edema, ulceration, erosion, and/or focal squamous epithelial degeneration of the non-glandular stomach were observed at 30 mg/kg/day GS-0976 alone and in all combination groups. The non-glandular stomach findings occurred in a dose-dependent manner were considered adverse in the 5/10 and 15/30 mg/kg/day SEL/GS-0976 groups. However, the findings do not have any relevance to humans since humans do not have a non-glandular stomach. In the lung, aggregates of macrophages, with or without interstitial mononuclear infiltrates and cholesterol clefts, were noted in all groups, including the vehicle

control group. While this finding was considered adverse in the high dose combination group due to increased incidence and severity, an increased occurrence after gavage dosing can also be indicative of mechanically induced reflux. The NOAEL for this study that is relevant to human safety is the 5/10 mg/kg/day SEL/GS-0976 group with corresponding SEL and GS-0976 exposure margins of 5 and 36-times above the clinical exposures, respectively.

In a 13-week repeat dose combination toxicity study in monkeys, SEL and GS-9674 when administered separately or in combination resulted in no adverse findings. Observed findings with the combination (increases in platelets, shortened prothrombin time (PT) and activated partial thromboplastin time (aPTT), increases in alkaline phosphatase, decreases in serum bile acids, increases in liver weight and hepatocellular hypertrophy) were non-adverse and attributed to GS-9674 and were consistent with those observed with GS-9674 administered alone. There was no exacerbation of the findings when GS-9674 was dosed in combination with SEL. The NOAEL for the combination was 10/300 mg/kg/day SEL/GS-9674, the highest dose group tested. Exposures of SEL and GS-9674 in the highest combination group were 2- and 34-fold higher, respectively, than the clinical exposures.

1.5.2. Clinical Trials

1.5.2.1. Study GS-US-402-2101: A Phase 1 Study to Evaluate Potential Drug-Drug Interactions Between GS-9674, SEL, and GS-0976

Study GS-US-402-2101 is a Phase 1, open-label, multiple-cohort, multiple-dose study designed to evaluate potential drug-drug interactions between SEL 18 mg, GS-9674 100 mg, and GS-0976 20 mg in healthy subjects (Cohorts 3-5). Cohorts 1 and 2, designed to evaluate potential combination DDIs using a lower dose of GS-9674, and Cohort 6, designed to evaluate the potential DDIs between all three agents, were not conducted based on preliminary data from Cohorts 3 through 5. A total of 108 subjects were enrolled in Cohorts 3 through 5.

1.5.2.1.1. Subject Disposition and Demographics

A total of 108 subjects were enrolled; 104 subjects completed study treatment. Four subjects prematurely discontinued study treatment, with 1 subject prematurely discontinuing due to an AE. Two subjects withdrew consent and 1 subject was lost to follow-up.

1.5.2.1.2. Safety Results

Administration of SEL, GS-0976 and GS-9674 was generally well tolerated in healthy subjects. No deaths, SAEs, Grade 4 AEs, or pregnancies were reported during this study. One subject experienced a Grade 3 AE of increased blood creatine phosphokinase during GS-9674 treatment that led to the discontinuation of study drug; this event was considered related to study drug by the investigator.

A total of 31 of 108 subjects (28.7%) experienced at least 1 AE, and the most commonly reported AEs overall were headache (9 subjects, 8.3%), constipation (4 subjects, 3.7%), and dizziness (3 subjects, 2.8%). No trends in the overall frequency or type of AEs across the cohorts or between the single-agent and combination treatments within the cohorts in this small number of subjects were observed.

Overall, 24 of 108 subjects (22.2%) experienced an AE that was considered to be related to study drug by the investigator. The most commonly reported study drug-related AEs overall were headache (8 subjects, 7.4%), constipation (4 subjects, 3.7%), and dizziness (3 subjects, 2.8%). With the exception of a Grade 3 AE of increased blood creatine phosphokinase, all other study drug-related AEs were Grade 1 in severity and did not require modification of study drug dose.

A total of 70 of 108 subjects (64.8%) experienced a graded laboratory abnormality. The majority of laboratory abnormalities were Grade 1 or 2 in severity, and no Grade 4 laboratory abnormalities were observed. 7 of 108 subjects (6.5%) had a Grade 3 laboratory abnormality: increased LDL cholesterol (5 subjects), increased creatine phosphokinase (1 subject), and occult blood in urine (1 subject). All subjects who had a Grade 3 increased LDL cholesterol had Grade 1 or 2 LDL cholesterol at baseline and at all other on-study measurements. The Grade 3 laboratory abnormality of increased creatine phosphokinase was associated with an AE that led to discontinuation of study drug. The Grade 3 laboratory abnormality of occult blood in urine was not associated with an AE and was considered not clinically significant by the investigator.

No notable changes in vital sign measurements or clinically significant ECG abnormalities were observed during the study.

1.5.2.1.3. Summary of PK Results

The changes in the primary PK parameters for SEL, GS-9674, and GS-0976 and their respective metabolites (GS-607509, GS-716070, and GS-834773) following once-daily administration of SEL, GS-9674, and/or GS-0976 in combination for 7 days compared with the single agent for 7 days are summarized in the Table 1-6. None of modest changes observed were considered clinically significant, and no dose modifications were needed upon co-administration of SEL, GS-9674, and/or GS-0976.

Table 1-6. GS-US-402-2101: Changes in primary PK parameters for SEL, GS-9674, and GS-0976 and their respective metabolites (GS-607509, GS-716070, and GS-834773) following once daily administration of SEL, GS-9674, and/or GS-0976 in combination for 7 days compared with the single agent for 7 days

Cohort 3: SEL+GS-0976	**GS-0976**	**GS-834773**	**SEL**	**GS-607509**
AUC_{tau}	↔	↔	↔	↔
C_{max}	↔	↔	↔	↔
C_{tau}	↑ 38%	↑ 69%	↔	↓ 9%
Cohort 4: GS-9674+SEL	**GS-9674**	**GS-716070**	**SEL**	**GS-607509**
AUC_{tau}	↔	↔	↔	↑ 28%
C_{max}	↑ 25%	↑ 26%	↔	↑ 28%
C_{tau}	↑ 25%	↔	↔	↑ 24%
Cohort 5: GS-9674+GS-0976	**GS-9674**	**GS-716070**	**GS-0976**	**GS-834773**
AUC_{tau}	↔	↔	↔	↔
C_{max}	↔	↔	↔	↔
C_{tau}	↑ 59%	↑ 24%	↓ 24%	↑ 3%[a]

The 90% CIs of the %GLSM ratios for test versus reference treatments were within (↔), extended above (↑), or extended below (↓) the predefined lack of PK alteration boundaries of 70% to 143%. Percentages indicate the increase or decrease in the geometric mean for the respective PK parameter for test treatment relative to reference treatment.

a The 90% CIs of the %GLSM ratio for test versus reference treatment extended both above and below the predefined lack of PK alteration boundaries of 70% to 143%.

1.5.2.2. Study GS-US-384-3914: A Proof of Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Regimens in Subjects with Nonalcoholic Steatohepatitis (NASH)

Study GS-US-384-3914 is an ongoing proof of concept, open-label, multiple-cohort study designed to evaluate the safety and efficacy of SEL 18 mg, GS-0976 20 mg, and GS-9674 30 mg alone and in combination in subjects with NASH. Cohorts 1 through 6 include subjects with NASH and stage 2 to 3 fibrosis as evaluated by a MRE ≥ 2.88 kPa and an MRI-PDFF ≥ 10% or a historical biopsy (by NASH CRN criteria or equivalent) within 12 months of Screening. Cohorts 1 through 3 are monotherapy cohorts, and Cohorts 4 through 6 are combination cohorts. Cohorts 7 and 8 includes subjects with cirrhosis due to NASH as evaluated by MRE ≥ 4.67 kPa, FibroScan® ≥ 14 kPa, FibroTest® ≥ 0.75, or a historical biopsy consistent with stage 4 fibrosis (by NASH CRN criteria or equivalent) within 12 months of Screening. All cohorts were planned to receive study drug for 12 weeks duration.

1.5.2.2.1. Cohort 1 (SEL), Cohort 2 (GS-0976) and Cohort 3 (GS-9674) Subject Disposition and Demographics

As of January 12, 2018, a total of 30 subjects were enrolled (N=10 for each cohort) and all had completed study treatment. No subjects prematurely discontinued study drug, withdrew consent, or were lost to follow-up.

1.5.2.2.2. Preliminary Safety Results

Fifty percent (50% [5/10]) of subjects had a TEAE in Cohorts 1 and 3, and 60% (6/10) of subjects had an AE in Cohort 2. There were no Grade 3 or 4 AEs, and no SAEs. In Cohort 1 and Cohort 2, the most common AEs occurred in the system organ class of GI disorders, with 20% (2/10) of subjects in each cohort experiencing this type of AE. In Cohort 3, the system organ class of infections and infestations included the most common AEs at 40% (4/10).

One subject in Cohort 1 had a Grade 4 hyperuricemia. There was one subject in Cohort 2 who had a Grade 3 lab abnormality of hypertriglyceridemia. There was one subject in Cohort 1 and two subjects in Cohort 3 who had Grade 3 hyperglycemia. One subject in Cohort 2 had a Grade 3 elevation of ALT and AST (Study Day 112), after stopping the study drug at Day 84. This was in the context of a viral illness. There was no concurrent increase in bilirubin or INR, and the ALT and AST decreased on repeat testing. In Cohort 3, there were two subjects with Grade 3 ALT and AST. These subjects' lab abnormalities were not associated with changes in bilirubin or INR. The subjects were asymptomatic and continued study drug with a decrease in their liver biochemistry while on treatment.

1.5.2.2.3. Cohort 4 (SEL + GS-9674), Cohort 5 (SEL + GS-0976) and Cohort 6 (GS-0976 + GS-9674) Subject Disposition and Demographics

As of January 12, 2018, a total of 60 subjects were enrolled (N=20 for each cohort). In Cohorts 4 and 5, all subjects had completed treatment. In Cohort 6, 16 subjects had completed study drug dosing, and the remaining 3 subjects had been dosed for at least 8 weeks. No subjects have prematurely discontinued study drug due to AE. One subject in Cohort 6 withdrew consent on Day 62, but this was not related to an AE.

1.5.2.2.4. Preliminary Safety Results

In Cohort 4, 25% (5/20) of subjects experienced a TEAE, and one subject had a Grade 3 treatment-emergent SAE (TESAE). This serious event was cellulitis and was not-related to study drug. In Cohort 5, 40% (8/20) of subjects experienced a TEAE, but these were all Grade 1 or 2. One subject had a Grade 2 SAE of a tooth abscess that was not-related to study drug. In Cohort 6, 50% (10/20) of subjects experienced an AE. Most of these AEs were Grade 1 or 2, and one subject experienced a Grade 3 serious event of a urinary tract infection (UTI), which was deemed not-related to study drug. The most common AEs were in the system organ class of infections and infestations (15%, 3/20) for Cohort 4, GI disorders for Cohort 5 (20%, 4/20), and infections and infestations (25%, 5/20) for Cohort 6.

No subjects in Cohorts 4 through 6 have discontinued study drug due to AEs. One subject in Cohort 6 had an interruption of drug while hospitalized due to the AE of a UTI. This UTI was exacerbated by excessive diuresis and subsequent electrolyte abnormalities, nausea, and dizziness. None of these events were deemed related to the study drug, and the subject continued on study drug after initiating treatment for the UTI.

Cohorts 4 and 5 each had two subjects (10%, 2/20) with Grade 3 hyperglycemia. One subject in Cohort 5 had an asymptomatic Grade 3 elevation in GGT with no concurrent elevation in other liver biochemistry laboratory values. In Cohort 6, 10% (2/20) of subjects have had Grade 3 hypertriglyceridemia. In Cohort 5 10% (2/20) of subject have had Grade 4 hypertriglyceridemia. All subjects were asymptomatic and were started on lipid lowering medication (fish oil or fibrate) with a decrease in their triglyceride levels.

The safety parameters in the 6 cohorts for this study as of January 12, 2018 have demonstrated that there is no clinically significant increase in the percentages of AEs (Table 1-7) or Grade 3 or above lab abnormalities (Table 1-8) for any combination of study drugs compared to the monotherapy. There has been one SAE in each of Cohort 4, Cohort 5, and Cohort 6, but these have been unrelated to study drug and not resulted in the discontinuation of either subject from the study. Grade 3 or above triglyceride elevations have been present in both monotherapy and combination cohorts including GS-0976 in similar percentages and all subjects have been asymptomatic.

1.5.2.2.5. Cohort 7 (GS-0976) and Cohort 8 (GS-9674) Subject Disposition and Demographics

As of January 12, 2018, a total of 20 cirrhotic subjects were enrolled (N=10 for each cohort). In Cohort 7, 10 subjects had completed 12 weeks of study drug. In Cohort 8, 8 subjects had completed 12 weeks of treatment, and the remaining 1 ongoing subject had taken at least 8 weeks of study drug. One subject in Cohort 8 prematurely discontinued study drug due to an AE.

1.5.2.2.6. Preliminary Safety Results

In Cohort 7, 80% (8/10) subjects experienced a treatment emergent AE, and one of these was a Grade 3 SAE of intestinal obstruction that was deemed not-related to study drug. In Cohort 8, 70% (7/10) subjects experienced a treatment emergent AE, and all of these were Grade 1 or 2 in severity. In Cohort 8, one subject experienced Grade 2 worsening of pruritus that led to study drug discontinuation. In Cohort 7, the largest percentage of AEs occurred in the system organ class of infections and infestations (30%, 3/10). In Cohort 8, the system organ classes of skin and subcutaneous tissue disorders and GI disorders both had the largest incidence (30%, 3/10 for each class).

In Cohort 7, 4 subjects (40%) experienced Grade 3 laboratory abnormalities. One subject had a transient decrease in their neutrophils. Two subjects had hyperglycemia, and one of these hyperglycemia subjects had concurrent Grade 3 hyponatremia that resolved with improved glycemic control. One subject had asymptomatic hypertriglyceridemia that resolved with fibrate

treatment. In Cohort 8, 3 subjects (30%) had Grade 3 lab abnormalities. One subject had a transient hypophosphatemia and one subject had hyperglycemia. One subject had an increase in their INR on Day 84 that was believed to be a lab error and normalized on repeat testing without intervention. Also, there were no concurrent changes in liver biochemistry testing with this transient increase in INR.

The safety parameters of these subjects demonstrate that both GS-0976 and GS-9674 can be dosed safely in subjects with cirrhosis due to NASH for 12 weeks duration. The single SAE in these cohorts was not-related to study drug GS-0976, and the subject who discontinued GS-9674 had Grade 2 worsening of pre-existing pruritus. The laboratory abnormalities of hyperglycemia and hypertriglyceridemia were due to poor baseline metabolic control and were asymptomatic. There are no clinically significant trends in safety parameters when comparing subjects with moderate fibrosis (ie, Cohorts 2 and 3) and cirrhosis (ie, Cohorts 7 and 8) in terms of AEs (Table 1-7) or Grade 3 or above lab abnormalities (Table 1-8) dosed with either GS-0976 or GS-9674.

Table 1-7. GS-US-384-3914: Safety Summary

n (%)	Cohort 1 SEL (N=10)	Cohort 2 GS-0976 (N=10)	Cohort 3 GS-9674 (N=10)	Cohort 4 SEL+ GS-9674 (N=20)	Cohort 5 SEL+ GS-0976 (N=20)	Cohort 6 GS-0976+ GS-9764 (N=20)	Cohort 7 GS-0976 [F4] (N=10)	Cohort 8 GS-9674 [F4] (N=10)
TEAEs	5 (50%)	6 (60%)	5 (50%)	5 (25%)	8 (40%)	10 (42.9%)	8 (80%)	7 (70%)
TEAEs Grade 3 or above	0	0	0	1 (5%)*	0	1 (5%)+	1 (10%)#	0
TESAEs	0	0	0	1(5%)*	1(5%)@	1 (5%)+	1 (10%)#	0
Treatment D/C due to AE	0	0	0	0	0	0	0	1 (10%)^

* Unrelated cellulitis from an insect bite
\+ Unrelated urinary tract infection
\# Unrelated intestinal obstruction
^ Grade 2 worsening pruritus
@ Unrelated tooth abscess

Table 1-8. GS-US-384-3914: Treatment-Emergent Grade 3 and 4 Lab Abnormality Summary

n (%)	Cohort 1 SEL (N=10)	Cohort 2 GS-0976 (N=10)	Cohort 3 GS-9674 (N=10)	Cohort 4 SEL+ GS-9674 (N=20)	Cohort 5 SEL+ GS-0976 (N=20)	Cohort 6 GS-0976+ GS-9764 (N=20)	Cohort 7 GS-0976 [F4] (N=10)	Cohort 8 GS-9674 [F4] (N=10)
Total	2 (20%)	2 (20%)	4 (40%)	2 (10%)	4 (20%)	2 (10%)	4 (40%)	3 (30%)
ALT	0	1 (10%)	2 (20%)	0	0	0	0	0
AST	0	1 (10%)	2 (20%)	0	0	0	0	0
GGT	0	0	0	0	1 (5%)	0	0	0
Urate	1 (10%)	0	0	0	0	0	0	0
Triglycerides	0	1 (10%)	0	0	2 (10%)	2 (10%)	1 (10%)	0
Glucose	1 (10%)	0	2 (20%)	2 (10%)	2 (10%)	0	2 (20%)	1 (10%)
Neutrophils (Decreased)	0	0	0	0	0	0	1 (10%)	0
Hypophosphatemia	0	0	0	0	0	0	0	1 (10%)
Hyponatremia	0	0	0	0	0	0	1 (10%)	0
Increased INR	0	0	0	0	0	0	0	1 (10%)

1.6. 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 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 needed to achieve optimal therapeutic benefit, particularly in patients with advanced fibrosis.

ASK1 inhibition with SEL reduces oxidative stress-induced hepatocyte apoptosis, inflammation and fibrogenesis by reducing activation of JNK and p38 stress-response kinases. Thus, SEL is postulated to halt several instigating triggers for NASH. ASK1 inhibition reduces hepatic steatosis and fibrosis in obese mice fed a fat and carbohydrate rich diet, and reduces liver fibrosis

in rats fed a choline-deficient, high-fat diet. In a completed Phase 2 study in subjects with NASH (GS-US-384-1497), SEL dose-dependently reduced liver fibrosis, demonstrating that ASK1 inhibition causes regression of liver fibrosis in humans. Increased rates of hepatic DNL and insufficient fatty acid oxidation lead to hepatic steatosis and associated lipotoxicity, which are also implicated in the etiology and progression of NASH. By inhibiting ACC, GS-0976 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), GS-0976 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 GS-9674 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), GS-9674 led to statistically significant reductions in hepatic steatosis and GGT, and thus, GS-9674 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 ASK1 inhibitor and ACC inhibitor, ASK1 inhibitor and FXR agonist, and 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 SEL and GS-9674, SEL and GS-0976, or GS-9674 and GS-0976.

NASH with fibrosis is a condition with a high risk of progression to cirrhosis which may lead to end-stage liver disease and increases the risk of HCC. Thus, reversing the fibrotic process in addition to ameliorating the metabolic dysfunction that drives NASH pathogenesis is paramount to improving the prognosis of this condition.

The current gold standard for assessing fibrosis is liver biopsy. As such, improvement in liver fibrosis without worsening of NASH as assessed by liver biopsy will be evaluated as the primary efficacy parameter in this 48-week study. However, liver biopsy has numerous limitations including its invasiveness and the potential for serious complications, which deter many patients from seeking evaluation for NAFLD or enrolling in clinical trials of novel therapies. Liver biopsy is also limited by cost, sampling error, and variability in histopathological interpretation. Due to these limitations, the development and validation of noninvasive markers of liver injury has emerged as a clinical and research priority. To further the development of such tools, this study will also incorporate noninvasive endpoints for the assessment of fibrosis including serum markers (eg, ELF™ test, FibroSURE/FibroTest®, pro-C3) and imaging (eg, liver stiffness by FibroScan® and MRE). Noninvasive markers of other histological lesions such as hepatic fat by MRI-PDFF and hepatocellular apoptosis by CK18 will also be measured. A key exploratory objective of the study is to correlate these markers with liver histology at baseline and determine their utility for monitoring histological responses that occur during the course of the study. Moreover, a subset of patients will be enrolled in the study based entirely on noninvasive markers of fibrosis; specifically a liver stiffness by FibroScan® XL probe ≥ 14.0 kPa and ELF™ test score ≥ 9.8 during screening. These criteria have been selected to increase the likelihood of enrolling patients with advanced fibrosis (F3-F4) rather than those with mild fibrosis (F0-F2), in

whom the urgency for treatment is lower {Miele 2017, Shadab Siddiqui 2017}. This novel approach will help inform the design of future clinical trials in NASH based entirely on noninvasive parameters for enrollment and the evaluation of treatment response.

1.6.1. Rationale for Dose Selection of SEL

SEL 18 mg once daily was selected for evaluation in this study based on a combination of safety and efficacy data in the Phase 2 NASH study (GS-US-384-1497) as well as PK/PD modeling of predicted inhibition of p38 phosphorylation. In study GS-US-384-1497, SEL 6 mg and 18 mg (± SIM 125 mg) for 24 weeks were evaluated. While both doses demonstrated a ≥ 1-stage decrease in NASH CRN fibrosis stage from baseline at a rate higher than subjects treated with SIM alone (20%) or compared to historical placebo response rates, SEL 18 mg (± SIM 125 mg) had a slightly higher response rate (43%) than SEL 6 mg (± SIM 125 mg) (30%). In addition, an exposure-response relationship was identified for SEL exposure and percent change from baseline of blood phosphorylated p38 measured in subjects in Phase 2 studies in PAH and DKD after administration of SEL 2 mg, 6 mg, or 18 mg once daily. Utilizing this model, plasma SEL AUC_{tau} observed in the NASH subjects after administration of SEL 18 mg ± SIM 125 mg was associated with 78% (7.5%) of maximal inhibition (E_{max}) of phosphorylated p38 [mean (%CV)]. A study of SEL in subjects with cirrhosis and hepatic impairment demonstrated no clinically relevant differences in SEL exposure which allows for treatment without dose adjustment in patients with advanced fibrosis. Across the clinical development program, SEL has been well-tolerated in Phase 1 and Phase 2 studies up to 48 weeks in duration with no clear dose-safety relationships for incidences or severity of AEs or laboratory abnormalities. Thus, the efficacy and safety profile of SEL support dosing of 18 mg once daily in this study.

1.6.2. Rationale for Dose Selection of GS-0976

The dose of GS-0976 chosen for evaluation in this study, 20 mg QD, is supported by the safety, tolerability and effects of GS-0976 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 GS-0976 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 GS-0976 up to 1000 mg or multiple daily doses (10 days) of GS-0976 up to 200 mg were administered. In healthy but overweight or obese subjects, a single GS-0976 dose of 20 mg resulted in a mean inhibition of fractional DNL of 71%. In study GS-US-426-3989, GS-0976 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. GS-0976 20 mg also had larger reductions in liver biochemistry (ie, ALT) and serum markers of fibrosis (ie, TIMP-1 and 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 GS-0976 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. GS-0976 exposures in non-cirrhotic subjects are expected to remain > 48- and 206-fold lower than the GS-0976 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, GS-0976 exposures in subjects with mild hepatic impairment (CP A) are expected to remain ≥ 22 and ≥105-fold lower than the GS-0976 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 GS-0976, dose adjustments are not considered necessary for subjects with compensated cirrhosis in this study.

1.6.3. Rationale for Dose Selection of GS-9674

A GS-9674 dose of 30 mg administered without regard to food has been selected for this study based on PK, PD, safety, and efficacy data from Phase 1 studies in healthy subjects and subjects with hepatic impairment (GS-US-402-1851, GS-US-454-4315, and GS-US-402-3885) and Phase 2 studies in subjects with NASH with or without cirrhosis (GS-US-402-1852 and GS-US-384-3914). GS-9674 exposure at this dose is expected to provide sufficient FXR agonism and result in histologic improvements in subjects with NASH.

In the Phase 1 study GS-US-402-1851, GS-9674 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 GS-9674 doses evaluated, doses ≥ 30 mg provided comparable intestinal FXR agonism as assessed by increases in FGF19 exposure. Food effect data in studies GS-US-402-1851 and GS-US-454-4315 shows that fasted exposure is contained within the range of exposures observed across meal types.

In ongoing studies, subjects with stage 1 to 3 fibrosis and compensated cirrhosis due to NASH have been dosed with 30 mg GS-9674 for 12 weeks with food, without regard to meal type. In non-cirrhotic NASH subjects 30 mg GS-9674 was well tolerated and associated with significant decreases in hepatic fat as assessed by MRI-PDFF and liver biochemistry (ie, GGT) over 12 weeks (GS-US-384-3914). Though GS-9674 exposures are increased in mild hepatic impairment (1.8-fold), GS-9674 30 mg was well tolerated following 12 weeks of treatment in subjects with compensated cirrhosis due to NASH (GS-US-384-3914). Additionally, adequate exposure margins (12- to 30-fold relative to preclinical NOAEL exposures) are expected after 30 mg GS-9674 administration to subjects with compensated cirrhosis due to NASH. Data supports that no GS-9674 dose adjustment is required for compensated cirrhosis in this study.

1.6.4. Rationale for Dose Selection of Combinations

SEL, GS-9674, and GS-0976 can be co-administered without dose modification. This is based on the available preclinical and clinical safety information of each single agent, as well as the combinations. The PK results from study GS-US-402-2101 showed no clinically meaningful changes in SEL, GS-9674, and GS-0976 exposure when co-administered (Section 1.5.2.1). In study GS-US-384-3914 described above (Section 1.5.2.2), combinations of SEL 18 mg once daily, GS-9674 30 mg once daily, and GS-0976 20 mg once daily, alone or in combination, were dosed in subjects with mild to advanced fibrosis due to NASH, with safety profiles that are similar to the monotherapies.

1.7. Risk/Benefit Assessment for the Study

This study will provide information regarding the safety and efficacy of SEL, GS-0976, GS-9674, alone or in combination for the treatment of patients with bridging fibrosis and compensated cirrhosis due to NASH. These patients are at the highest risk for clinical complications related to their liver disease. As there are currently no approved therapies for NASH, there is a large unmet medical need for this growing population of patients.

The potential benefits of SEL for the treatment of NASH were shown in the Phase 2 study GS-US-384-1497. As described above, fibrosis regression was observed in a greater proportion of SEL-treated versus SIM-treated subjects after only 24 weeks of treatment. Although this study did not include a placebo control arm, these response rates to SEL are substantially higher than reported in the placebo groups of Phase 2 trials for other compounds in development for NASH {Neuschwander-Tetri 2014, Ratziu 2016}. In addition, reductions in liver biochemistries (eg, ALT, AST, GGT), liver fat content by MRI-PDFF, lobular inflammation, liver stiffness by MRE, and biomarkers of apoptosis and necrosis (serum CK-18 M30 and M65 levels) were observed, particularly in fibrosis responders.

The potential benefits of GS-0976 for the treatment of NASH were shown in the Phase 2 study GS-US-426-3989. As described above, significant and clinically meaningful reductions in hepatic fat by MRI-PDFF and decreases in ALT, TIMP-1, and PIIINP were observed in the subjects who received GS-0976 20 mg for only 12 weeks of treatment. Based on these results, improvements in liver histology including hepatic fibrosis would be expected to ensue in studies of longer duration. A subset of subjects who received GS-0976 in the Phase 2 study had asymptomatic Grade 3 or 4 elevations in triglycerides that resolved spontaneously or with treatment with fibrates or fish oil. These subjects had abnormal triglycerides at baseline, and so strategies to mitigate this risk in the proposed study will consist of exclusion criteria for triglyceride elevations above 250 mg/dL and close monitoring of lipid testing with a plan to initiate treatment with fibrates or fish oil if clinically indicated (see Figure 7-3).

Subjects randomized to GS-9674 may benefit from an improvement in their underlying NASH which may manifest as improvements in liver biochemistry, hepatic steatosis, and fibrosis. In the proof of concept study (GS-US-384-3914), 10 subjects with mild to moderate fibrosis and 10 subjects with cirrhosis due to NASH have been dosed with GS-9674 for 12 weeks. These subjects have shown decreases in hepatic fat by MRI-PDFF and liver biochemistry (ie, GGT). One subject with cirrhosis discontinued the study due to worsening pruritus, and to mitigate this potential risk with GS-9674, close monitoring of clinical signs and symptoms with a plan to initiate treatment for pruritus if clinically indicated has been recommended (see Section 7.5.5). In the Phase 1 study, 94 subjects have received GS-9674 in single or multiple doses (14 days) up to 300 mg. All TEAEs were mild to moderate (Grade 1 or 2), and overall, the rate of any AEs was similar between subjects treated with GS-9674 or placebo. The predominant toxicities were anemia, back pain, diarrhea, and headache. Grade 2 or 3 elevations in serum ALT were seen in five (5%) GS-9674 treated subjects and one (4%) placebo treated subject. Grade 2 or 3 ALT elevations that occurred on-treatment were observed in 2/23 (9%) twice daily (BID) treated subjects, but none of the 71 subjects who received QD GS-9674 dosing. In these cases,

elevations in serum bilirubin or prolongation of INR were not observed, serum ALT levels normalized upon treatment cessation, and no evidence of drug hypersensitivity syndrome (eg, fever, rash, eosinophilia) was noted. In nonclinical studies, effects on the liver have been limited to non-adverse mild increases in alkaline phosphatase and liver weights and minimal hepatocellular hypertrophy that are likely a pharmacological response to FXR agonism. There were no elevations in liver transaminases or changes in liver pathology (degeneration/necrosis) in the nonclinical studies to suggest direct cellular damage. In order to mitigate the potential risk of hepatotoxicity with GS-9674, QD dosing of GS-9674 has been chosen for this study. Moreover, close monitoring of liver biochemistry values will be performed and parameters for discontinuation of the study drugs due to liver test abnormalities have been defined (see Section 7.5) and will be closely followed.

Subjects with advanced fibrosis who are randomized to the placebo control arm in the study may benefit from frequent medical monitoring and close assessment of their NASH (eg, surveillance for HCC and hepatic decompensation) and associated pathologies during the duration of placebo treatment.

Additional risks to study subjects include those attributable to study participation in general, including risks associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include close monitoring of lab values as well as AEs. Parameters for discontinuation of the study drugs due to AEs and non-hepatic laboratory abnormalities are also defined and will be closely followed.

Overall, the nonclinical and preliminary clinical data show a positive benefit/risk ratio in support of the study in subjects with bridging fibrosis and compensated cirrhosis due to NASH. Appropriate safety monitoring will be conducted throughout the study to further characterize the safety profile of SEL, GS-0976, and GS-9674, alone or in combination, in this patient population.

In summary, there are no approved treatment options available for patients with NASH. Based on clinical experience with SEL, GS-0976, and GS-9674, alone or in combination, the risk/benefit ratio is positive and supports the continued evaluation of these monotherapies and combination therapies in this patient population.

1.8. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To assess the safety and tolerability of SEL, GS-0976, and GS-9674, administered alone or in combination, in subjects with bridging fibrosis or compensated cirrhosis due to NASH
- To evaluate changes in liver fibrosis, as measured by the NASH CRN classification, without worsening of NASH (defined as any increase in hepatocellular ballooning or lobular inflammation)

CCI

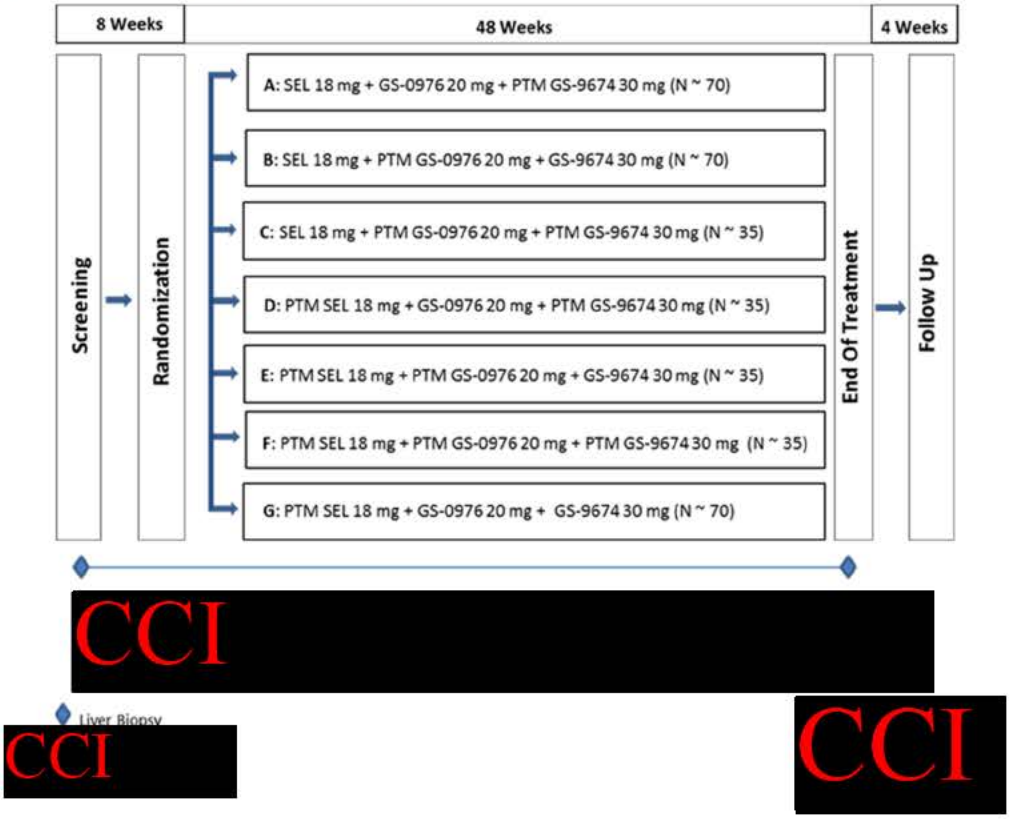
3. STUDY DESIGN

3.1. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of SEL, GS-0976, GS-9674, and combinations in subjects with bridging fibrosis or compensated cirrhosis due to NASH.

The overall study design is presented graphically in Figure 3-1.

Figure 3-1. Overall Study Design



3.2. Study Treatments

Subjects meeting the study's entry criteria will be assigned randomly in a 2:2:1:1:1:1:2 ratio to 1 of 7 treatment groups (Group A, Group B, Group C, Group D, Group E, Group F, or Group G), with approximately 70 subjects in each combination treatment group and approximately 35 subjects in each single agent or placebo group, as shown in Figure 3-1. Randomization will be stratified by the presence or absence of diabetes mellitus, as determined by medical history or based on the Screening lab values if previously undiagnosed (HbA1c $\geq$ 6.5% or fasting plasma glucose $\geq$ 126 mg/dL) and by the presence or absence of cirrhosis (F4) as determined by the central biopsy reader at Screening.

Study drugs will be administered for a total of 48 weeks from the Day 1 visit. Dosage and administration of the study drugs and reference products are described in Section 5.2.4.

3.3. Duration of Study

Participation can last up to 60 weeks, which includes an 8-week Screening period, a 48-week On-Treatment period, and a 4-week Follow-Up period.

3.4. End of Study

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

3.5. Post Study Care

There is no offered post study care.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will enroll approximately 350 subjects with bridging fibrosis and compensated cirrhosis due to NASH. Approximately 60% of the enrolled subject population will have cirrhosis on the Screening liver biopsy, and approximately 40% of these subjects will have cirrhosis due to NASH with < 5% steatosis. Approximately 70 subjects who do not have historical liver biopsies may be enrolled based on noninvasive fibrosis markers (FibroScan® and ELF™ Test score) regardless of fibrosis stage determined on the Screening liver biopsy.

4.2. Inclusion Criteria

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

1) Males and non-pregnant, non-lactating females between 18 – 80 years of age inclusive, based on the date of the Screening visit;

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

3) Bridging fibrosis or cirrhosis due to NASH as defined by one of the following; all subjects must not have documented weight loss > 5% between the date of the biopsy and Screening:

    a) NASH (defined as the presence of a steatosis grade ≥ 1, hepatocellular ballooning grade ≥ 1, and lobular inflammation grade ≥ 1, according to the NAS) and bridging fibrosis (F3) within 6 months of Screening, in the opinion of the central reader;

    b) Compensated cirrhosis (F4) due to NASH (defined as the presence of a steatosis grade ≥ 1, hepatocellular ballooning grade ≥ 1, and lobular inflammation grade ≥ 1, according to the NAS) within 12 months of Screening, in the opinion of the central reader;

    c) Compensated cirrhosis (F4) due to NASH with < 5% steatosis (defined as a steatosis grade of 0, hepatocellular ballooning grade ≥ 1, and lobular inflammation grade ≥ 1, according to the NAS) within 12 months of Screening, in the opinion of the central reader; and at least two of the following criteria for metabolic syndrome, modified from the NCEP ATP III, 2005 Guidelines at Screening:

        i) Fasting glucose ≥ 100 mg/dL or receiving drug treatment for elevated glucose;

        ii) Fasting HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women or receiving drug treatment for low HDL cholesterol;

        iii) Fasting triglycerides ≥ 150 mg/dL or receiving drug treatment for elevated triglycerides;

iv) Waist circumference ≥ 102 cm for men or ≥ 88 cm for women or BMI ≥ 30 kg/m^2;

v) Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or receiving drug treatment for hypertension;

d) In subjects who have never had a liver biopsy, liver stiffness by FibroScan® XL probe ≥ 14.0 kPa, Enhanced Liver Fibrosis (ELF™) Test score ≥ 9.8, and at least two of the criteria for metabolic syndrome modified from the NCEP ATP III Guidelines, at Screening. In subjects eligible based on this criterion, a liver biopsy must be performed during Screening and must be deemed evaluable for fibrosis stage and NAS by the central reader; however, the reported stage of fibrosis will not determine eligibility for the study;

4) Screening laboratory parameters, as determined by the central laboratory:

a) eGFR ≥ 60 mL/min, as calculated by the Cockcroft-Gault equation;

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

c) Hemoglobin ≥ 10.6 g/dL;

d) INR ≤ 1.4, unless due to therapeutic anticoagulation;

e) Total bilirubin ≤ 1.3 x ULN, unless due to an alternate etiology such as Gilbert's syndrome or hemolytic anemia;

f) Platelet count ≥ 125,000/µL;

g) Serum triglyceride level ≤ 250 mg/dL;

h) ALT < 5 x ULN;

5) BMI ≥ 18 kg/m^2 at Screening;

6) Female subjects of childbearing potential (see definition in Appendix 3) must have a negative pregnancy test at Screening and Day 1;

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) Known hypersensitivity to SEL, GS-0976, GS-9674, the metabolites, or formulation excipients;

2) Prior history of decompensated liver disease including ascites, HE, or variceal bleeding;

3) CP score > 6 at Screening, unless due to an alternate etiology such as Gilbert's syndrome or therapeutic anticoagulation;

4) MELD score > 12 at Screening, unless due to an alternate etiology such as therapeutic anticoagulation;

5) Chronic HBV infection (HBsAg positive);

6) Chronic HCV infection (HCV Ab and HCV RNA positive). Subjects cured of HCV infection less than 2 years prior to the Screening visit are not eligible;

7) Other causes of liver disease based on medical history and/or centralized review of liver histology, including but not limited to: alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders (eg, PBC, 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) Current or prior history of HCC;

10) Any weight reduction surgery within 2 years prior to Screening or malabsorptive weight loss surgery (eg, Roux-en-Y or distal gastric bypass) at any time prior to Screening. Weight reduction surgery is disallowed during the study;

11) Intestinal resection that could result in malabsorption of study drugs;

12) Weight loss > 10% within 6 months prior to Screening;

13) HIV infection;

14) History of symptomatic chronic pulmonary disease (eg, chronic obstructive pulmonary disease, interstitial lung disease) within 6 months prior to Screening;

15) 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 Screening;

    b) Transient ischemic attack or cerebrovascular accident within 6 months prior to Screening;

    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 Screening;

16) Males who habitually drink greater than 21 oz/week of alcohol or females who habitually drink greater than 14/oz week of alcohol (1 oz/30 mL of alcohol is present in: a 12 oz/360 mL beer, a 4 oz/120 mL glass of wine, and a 1 oz/30 mL measure of 40 proof alcohol);

17) Positive urine drug screen for amphetamines, cocaine or opiates (eg, heroin, morphine) at Screening. Subjects on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to Screening may be included in the study. Subjects with a positive urine drug screen due to prescription medication (eg, opioids, methylphenidate) are eligible if the prescription and diagnosis are reviewed and approved by the investigator;

18) Use of any prohibited concomitant medication as described in Section 5.3. 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 6 months prior to the diagnostic liver biopsy and subjects on antidiabetic medications must be on a stable dose for at least 3 months prior to the diagnostic liver biopsy;

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

    a) Adequately treated carcinoma in situ of the cervix;

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

20) Unable to safely undergo a liver biopsy;

21) Concurrent participation in another therapeutic clinical study;

22) Presence of any laboratory abnormality or condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, including a history of substance abuse and/or a psychiatric condition requiring hospitalization and/or emergency room visit within 2 years of Screening;

23) Unavailable for follow-up assessment or concern for subject's compliance with the protocol procedures.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Mobile/Web Response System (IXRS) will be used for centralized randomization and treatment assignment. Randomization will be stratified by the presence or absence of diabetes mellitus, as determined by medical history or based on the Screening lab values if previously undiagnosed (HbA1c ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dL), and the presence or absence of cirrhosis (F4) as determined by the central biopsy reader at Screening.

Investigative site personnel will obtain the subject's identification number and study drug assignment from the IXRS. Subjects and all personnel directly involved in the conduct of the study will be blinded to treatment assignment.

Study drugs will be dispensed in a blinded fashion to the subjects.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IXRS for that subject. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation, along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

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

In the event that GS-US-384-1943 and GS-US-384-1944 demonstrate lack of efficacy and are discontinued after the Week 48 Interim Analysis, unblinding of the SEL monotherapy treatment group will occur. Unblinded SEL monotherapy treatment assignments will be generated by the external reporting statistician. Investigators will receive subject-specific SEL monotherapy treatment assignments upon applicable regulatory authority and IRB/IEC/EC approval to discontinue subjects from study drug and complete assessments for premature discontinuation from study (refer to Section 6.8).

The rationale for unblinding must be clearly explained in source documentation, along with the date on which treatment assignment was obtained.

The Pharmacovigilance & Epidemiology (PVE) department at Gilead Sciences may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of SEL, GS-0976, GS-9674

5.2.1. Formulation

5.2.1.1. Selonsertib (SEL) 18 mg

SEL will be supplied as 18 mg strength tablets. The tablets are round, film-coated gray tablets debossed with an underscored "18" on one side and "GSI" on the other side. In addition to the active ingredient, SEL tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxide black.

PTM SEL tablets are identical in size, shape, color and appearance to their corresponding strength of active SEL tablets and contain the same inactive ingredients.

5.2.1.2. GS-0976 20 mg

GS-0976 will be supplied as 20 mg strength tablets. The tablets are round, plain-faced, film-coated white tablets containing 20 mg of GS-0976. In addition to the active ingredient, GS-0976 tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc, which are common pharmaceutical excipients.

PTM GS-0976 tablets are identical in size, shape, color and appearance to their corresponding strength of active GS-0976 tablets and contain the same inactive ingredients.

5.2.1.3. GS-9674 30 mg

GS-9674 will be supplied as 30 mg strength tablets. The tablets are capsule-shaped, plain-faced, film-coated orange tablets. The tablets contain GS-9674-02 (tromethamine salt) and inactive ingredients microcrystalline cellulose, mannitol, crospovidone, magnesium stearate, and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide, and ferrosoferric oxide.

PTM GS-9674 tablets are identical in size, shape, color, and appearance to their corresponding strengths of active GS-9674 tablets. PTM GS-9674 tablets contain the following ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide, and ferrosoferric oxide.

5.2.2. Packaging and Labeling

SEL and PTM SEL 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 fitted with an induction-sealed and aluminum-faced liner.

GS-0976 and PTM GS-0976 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.

GS-9674 and PTM GS-9674 tablets are packaged in white, HDPE bottles. Each bottle contains 30 tablets, a 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 drugs 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) and/or other local regulations.

5.2.3. Storage and Handling

SEL, PTM SEL, GS-0976, PTM GS-0976, GS-9674, and PTM GS-9674 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 drugs should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

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

5.2.4. Dosage and Administration

The administration of study drugs will be recorded in the source documentation and in the eCRF.

SEL, PTM SEL, GS-0976, PTM GS-0976, GS-9674, and PTM GS-9674 tablets will be provided by Gilead Sciences. Subjects will take one tablet of each drug (or PTM) together at approximately the same time each day. Drugs should be taken with or without food, and swallowed whole with water. A dose will be considered missed if the subject cannot take the complete 3 tablet 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.

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

- Treatment Group A: one SEL 18 mg tablet, one GS-0976 20 mg tablet, and one PTM GS-9674 30 mg tablet administered orally once daily with or without food
- Treatment Group B: one SEL 18 mg tablet, one PTM GS-0976 20 mg tablet, one GS-9674 30 mg tablet administered orally once daily with or without food
- Treatment Group C: one SEL 18 mg tablet, one PTM GS-0976 20 mg tablet, and one PTM GS-9674 30 mg tablet administered orally once daily with or without food
- Treatment Group D: one PTM SEL 18 mg tablet, one GS-0976 20 mg tablet, and one PTM GS-9674 30 mg tablet administered orally once daily with or without food
- Treatment Group E: one PTM SEL 18 mg tablet, one PTM GS-0976 20 mg tablet, and one GS-9674 30 mg tablet administered orally once daily with or without food
- Treatment Group F: one PTM SEL 18 mg tablet, one PTM GS-0976 20 mg tablet, and one PTM GS-9674 30 mg tablet administered orally once daily with or without food
- Treatment Group G: one PTM SEL 18 mg tablet, one GS-0976 20 mg tablet, and one GS-9674 30 mg tablet administered orally once daily with or without food

5.3. 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 Screening and any taken during the study until the end of the follow-up period.

Caution should be exercised when co-administering sensitive P-gp substrates with narrow therapeutic index (eg, digoxin) with study drugs, as it may increase the concentrations of these agents. The Investigator should review the prescribing information of the concomitant medication for guidance on co-administration with a weak P-gp inhibitor.

Subjects on Vitamin E ≥ 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 6 months prior to the diagnostic liver biopsy. Subjects on antidiabetic medication(s) must be on stable dose(s) for at least 3 months prior to the diagnostic liver biopsy. If possible, the doses of these medications should remain stable through the end of treatment.

Any investigational medication within 30 days or within 5 half-lives prior to Screening and throughout the study (eg, obeticholic acid, elafibranor, and cenicriviroc) is prohibited. Subjects enrolled in the current protocol may participate concurrently in a HepQuant™ sponsored investigational device study at participating US sites only (Investigational Device Exemption # G170034/S002), once approved by the applicable IRB/IEC.

The following medications are prohibited for all treatment groups, from 30 days prior to Day 1 up to and including the day of the last dose of study drugs:

- Chronic systemic immunosuppressants including but not limited to: corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (eg, infliximab). Use for ≤ 2 weeks total is allowed.
- Hematologic stimulating agents (eg, erythropoiesis-stimulating agents [ESAs]; granulocyte colony stimulating factor [GCSF]; thrombopoietin [TPO] mimetics)
- 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 representative medications that are prohibited or which should be used with caution are listed below in Table 5-1.

Table 5-1. List of Representative Disallowed and Use with Caution Medications[a]

Agents Disallowed	
Drug Class	**Disallowed 30 days prior to Day 1 through the end of treatment**
Immunosuppressants	Chronic systemic corticosteroids[b], tacrolimus, sirolimus, cyclosporine, mycophenolate mofetil, and methotrexate
Acid Reducing Agents	H2-Receptor antagonists[d]
Antibiotics[c]	azithromycin, clarithromycin, erythromycin
Anticonvulsants[c]	phenobarbital, phenytoin, carbamazepine, oxcarbazepine
Antimycobacterials[c]	rifamycins, isoniazid
Endothelian Receptor Antagonists[c]	Bosentan
Herbal/Natural Supplements[c]	St. John's Wort, Echinacea, milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Other[c]	gemfibrozil, modafinil
Agents to be used with Caution	
Drug Class	**Agents to be used with Caution from 30 days prior to Day 1 through end of treatment**
Cardiac Medications[e]	digoxin[f], dabigatran etexilate, aliskiren
Acid Reducing Agents	antacids[g]
Bile Acid Sequestrants[h]	cholestyramine, colestipol, colesevelem

a Not all of these example medications may be approved in each of the countries 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 May result in an increase or decrease in the concentration of study drugs.
d H2-Receptor antagonists can be taken up to 3 days prior to Day 1.
e SEL may increase the exposure of these medications.

f For subjects on digoxin at start of study: obtain digoxin level prior to starting study drug and at the Week 1 Visit with digoxin level checks during the study period per Investigator discretion. Monitor and adjust digoxin dose as necessary based on prescribing information.
g Antacids that directly neutralize stomach pH (ie, Tums, Maalox) are permitted but may not be taken within 4 hours (before or after) study drug administration.
h Bile acid sequestrants are permitted but may not be taken within 4 hours (before or after) study drug administration.

5.4. Accountability for SEL, GS-0976, and GS-9674

The Investigator is responsible for ensuring adequate accountability of all used and unused Investigational Medicinal Product (IMP). This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP dispensed to subjects must be returned to the site.

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

- Record the date received and quantity of IMP kits
- Record the date, subject number, the IMP kit number dispensed
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

5.4.1. Investigational Medicinal Product Return or Disposal

At the start of the study, the study monitor will evaluate the study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used (empty bottles) and unused study drug supplies performed in accordance with the site's (hospital/pharmacy) SOP. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies. A copy of the site's SOP will be obtained for central files. Where possible, study drugs will be destroyed at the site. Upon study completion, a copy of the Investigational Drug Accountability records must be filed at the site. Another copy will be returned to Gilead Sciences. If drug is destroyed on site, the Investigator must maintain accurate records for all study drug bottles destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug. All study drug records must be maintained at the site and copies must be submitted to Gilead Sciences at the end of the study.

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 Site Operations 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

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. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 8 weeks before randomization to determine eligibility for participation in the study. The Screening period may be extended under special circumstances with the explicit approval of the Gilead Medical Monitor.

Screening laboratory tests may be repeated once within the Screening period, at the discretion of the Investigator, prior to Randomization.

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

The following will be performed and documented at Screening:

- Obtain written informed consent prior to initiation of any Screening procedures
- Obtain Screening number from IXRS
- Obtain medical history
- Record all concomitant medications that the subject has taken within 30 days prior to Screening
- Complete PE
- Vital signs, body weight, and height
- [redacted]
- Assess ascites and HE

- 12-Lead ECG

[redacted]

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - Insulin and lipids
  - HIV-1, HBV, and HCV serology
  - HbA1c (if unable to be resulted, serum fructosamine will be tested)

[redacted]

[redacted]

  - Serum pregnancy test (for females of childbearing potential)

[redacted]

- Collect urine samples for:
  - Urine drug screen for amphetamines, cocaine and opiates (ie, heroin, morphine)

[redacted]

- Perform liver biopsy (if required) and provide liver tissue for central reading. A historical biopsy that meets eligibility criteria may be accepted as the Screening biopsy if the sample is deemed acceptable for interpretation by the central reader. The historical sample must be within 6 months of Screening for F3 subjects and within 12 months of Screening for F4 subjects.

[redacted]

- Record in the source documents and eCRFs all SAEs and any AEs related to protocol mandated procedures that occurred after signing of the consent form. 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.

- Confirm subject's liver histological findings, including fibrosis stage, on the centrally read biopsy report

[redacted]

- Review and document the subject's eligibility status

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic after Screening for randomization into the study.

6.3. Day 1 Assessments

All Day 1 assessments must be completed before subject dispensation/dosing of study drugs.

6.3.1. Day 1: Randomization and Assessments

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

After review of inclusion and exclusion criteria to confirm continued eligibility, subjects will be randomized to study drug assignment and receive a Subject Identification Number via the IXRS. CCI [redacted]

The following will be performed and documented at the Day 1 visit prior to dosing:

[redacted]

- Lifestyle questionnaire

[redacted]

- Symptom driven PE
- Vital signs and body weight

[redacted]

- Assess ascites and HE
- Provide lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - Insulin and lipids
  - HbA1c
  - [redacted]
  - [redacted]
  - [redacted]

    Note: For subjects on digoxin at start of study: obtain digoxin level prior to starting study drug and at the Week 1 Visit, with digoxin level checks during the study period per Investigator discretion. Monitor and adjust digoxin dose as necessary based on prescribing information.
- Collect urine samples for:
  - Albumin
  - Creatinine
  - Albumin/creatinine ratio
  - [redacted]
  - Pregnancy test (for females of childbearing potential only)
- [redacted]
- Record all concomitant medications that the subject has taken since the previous visit
- Record all SAEs and any AEs related to protocol mandated procedures occurring since the Screening visit

- Dispense study drugs and provide instruction on appropriate dosing and administration; subject will take the Day 1 dose of study drugs on-site at the end of the visit, with or without food

[redacted]

[redacted]

6.4. On-Treatment Assessments

6.4.1. Week 1 Visit (± 3 days)

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

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

- Lifestyle questionnaire

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

- Symptom driven PE
- Vital signs and body weight
- Assess ascites and HE
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - [redacted]

    Note: For subjects on digoxin at start of study: obtain digoxin level prior to starting study drug and at the Week 1 Visit, with digoxin level checks during the study period per Investigator discretion. Monitor and adjust digoxin dose as necessary based on prescribing information.

- Record all concomitant medications that the subject has taken since the previous visit
- Record all SAEs and any AEs occurring since the previous visit
- Review of study drug dosing compliance (pill count) and provide instruction on appropriate dosing and administration

[redacted]

[redacted]

6.4.2. Week 4, Week 12, and Week 36 Visits (±3 days)

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

The following will be performed and documented at this visit:

[redacted]

- Lifestyle questionnaire

[redacted]

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.

- Symptom driven PE
- Vital signs and body weight

[redacted]

- Assess ascites and HE
- Provide lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - Insulin and lipids
  - HbA1c

[redacted]

- Collect urine samples for:
  - Albumin (Weeks 12, 36)
  - Creatinine (Weeks 12, 36)
  - Albumin/creatinine ratio (Weeks 12, 36)
  - Biomarkers (Weeks 12, 36)
  - Pregnancy test (for females of childbearing potential only)
- Record all concomitant medications that the subject has taken since the previous visit
- Record all SAEs and any AEs occurring since the previous visit
- Review of study drug dosing compliance (pill count)
- Dispense study drug and provide instruction on appropriate dosing and administration

[redacted]

6.4.3. Week 8, Week 16, Week 20, Week 28, Week 32, Week 40, and Week 44 Visits (±3 days)

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

The following will be performed and documented at this visit:

- Lifestyle questionnaire

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

- Vital signs and body weight
- Symptom driven PE
- Assess ascites and HE
- Lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - [redacted]
  - [redacted]
- Collect urine samples for:
  - Pregnancy test (for females of childbearing potential only)
- Record all concomitant medications that the subject has taken since the previous visit
- Record any SAEs and all AEs occurring since the previous visit
- Review of study drug dosing compliance (pill count)
- Dispense study drugs to the subject and provide instruction on appropriate dosing and administration

[redacted]

[redacted]

6.4.4. Week 24 and Week 48 (±7 days)

[redacted]

- Lifestyle questionnaire

[redacted]

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

- Vital signs and body weight

- Complete PE
- Hip and waist circumference
- 12-lead ECG (Week 48 only)
- Assess ascites and HE
- Lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - Insulin and lipids
  - HbA1c
  - [redacted]
- Collect urine samples for:
  - Albumin
  - Creatinine

— Albumin/creatinine ratio

[redacted]

— Pregnancy test (for females of childbearing potential only)

[redacted]

- Liver biopsy and provide liver tissue for central reading (Week 48 only)
- Record all concomitant medications that the subject has taken since the previous visit
- Record all SAEs and any AEs occurring since the previous visit
- Review of study drug dosing compliance (pill count)
- Dispense study drug and provide instruction on appropriate dosing and administration (Week 24 **only**)

  Note: Subjects should not exceed the allowed dosing period of 48 weeks (336 days). All effort should be made for the Week 48 visit to coincide with the subject's last dose of study drug. If it is not possible to schedule the Week 48 visit on Day 336 of dosing, detailed dosing instructions should be provided to subjects on the precise day to complete their dosing before or after their Week 48 visit.

[redacted]

6.4.5. Early Termination (ET) Visit

[redacted]

- Lifestyle questionnaire

[redacted]

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.

- Complete PE

- Vital signs and body weight
- [redacted]
- 12-lead ECG
- Assess ascites and HE
- Lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - Insulin and lipids
  - HbA1c
  - ELF™ Test
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Collect urine samples for:
  - Albumin
  - Creatinine
  - Albumin/creatinine ratio
  - [redacted]
  - Pregnancy test (for females of childbearing potential only)

[redacted]

- Record all concomitant medications that the subject has taken since the previous visit
- Record all SAEs and any AEs occurring since the previous visit
- Review of study drug dosing compliance (pill count)
- At the discretion of the Investigator, perform the following assessments:

  [redacted]

  [redacted]

  — Liver biopsy and provide liver tissue for central reading

[redacted]

[redacted]

6.4.6. 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
- Obtain blood samples for:

  — Chemistry

  — Hematology

  — eGFR

- Record vital signs and body weight
- Record all concomitant mediations that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events occurring since the previous visit

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

6.5. Post-treatment Assessments

6.5.1. Follow-Up Visit (±5 days)

Subjects will return for a Follow-Up visit four weeks after the date of last dose of study drug.

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

The following will be performed and documented at this visit:

- Symptom driven PE
- Vital signs and body weight
- [redacted]
- 12-lead ECG
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation
  - Insulin and lipids
  - HbA1c
  - [redacted]
- Collect urine samples for:
  - [redacted]
  - Albumin
  - Creatinine
  - Albumin/creatinine ratio
  - Pregnancy test (for females of childbearing potential only)

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

[redacted]

6.6. Criteria for Discontinuation of Study Drug

Study drugs must be discontinued in the following instances:

- 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 as defined in Appendix 4) 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

[redacted]

- 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 or treatment groups at the request of Gilead, a regulatory agency, or an IRB/IEC/EC.

6.7. Interruption of Study Drug

If dosing is interrupted (ie, as a result of an AE), the subject must stop dosing of all three 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.

6.8. Assessments for Premature Discontinuation from Study

Subjects prematurely discontinuing from the study (eg, as a result of an AE or a treatment group closure) should have an ET visit upon discontinuing, as well as a Follow-Up visit 4 weeks after the date of the last dose of study drugs (refer to Section 6.4.5 and 6.5.1). Discussion with the Medical Monitor is recommended.

The subject will be considered off-study after the completion of these visits.

If these visits are not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study.

CCI [redacted]

CCI [redacted]

6.11. Description of Assessments

6.11.1. Clinical Laboratory Analytes

Fasting is required prior to all study visits. Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the visit to ensure an approximate 8-hour fast prior to the blood sample collection the next morning. Please refer to the Covance Laboratory Manual or the individual subject Covance laboratory report for gender and age specific reference ranges.

Chemistry:

CCI , bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, insulin, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, CCI , total protein, uric acid, CCI , eGFR as calculated by the Cockcroft-Gault equation, and creatine phosphokinase (CPK)

Hematology:

Hematocrit (Hct), hemoglobin (Hgb), 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, PT, and activated partial thromboplastin time (APTT)

Additional Tests:

HIV-1 antibody (reflex to HIV-1 RNA), HBV (HBsAg), HCV antibody (reflex to HCV RNA), serum pregnancy testing, FSH, eGFR as calculated by MDRD, homeostasis model assessment of insulin resistance (HOMA-IR, based on fasting glucose and insulin), C-peptide, lipid panel (cholesterol, high-density lipoprotein [HDL], LDL, triglycerides, and other lipid tests), free fatty acids, digoxin testing, HbA1c (serum fructosamine will be tested if HbA1c is unable to be resulted)

CCI [redacted]

Urine Samples:

Urine will be collected for albumin, creatinine, albumin/creatinine ratio, drug screening (for amphetamines, cocaine, methadone, and opiates), pregnancy testingCCI [redacted]

CCI [redacted]

6.11.2. Physical Examination

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

The focus of a symptom driven PE will be determined by the Investigator based on subject complaint. 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.

All complete and symptom driven examinations should include assessments to determine the presence of ascites and HE, and a pulmonary examination with questioning regarding pulmonary symptoms.

6.11.3. Vital SignsCCI [redacted]

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

Blood pressure will be measured using the following standardized process:

- 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 millimeter of mercury (mmHg) mark on the manometer or to the nearest whole number on an automatic device.

CCI [redacted]

[redacted]

6.11.4. Medical History

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

6.11.6. Creatinine Clearance

Creatinine clearance will be calculated by the Central Laboratory, using the Cockcroft-Gault equation {Cockcroft 1976}.

$$\text{Male: } CL_{cr}\ (\text{mL/min}) = \frac{[140 - \text{age (years)}] \times BW(\text{kg})}{72 \times S_{cr}}$$

$$\text{Female: } CL_{cr}\ (\text{mL/min}) = \frac{[140 - \text{age (years)}] \times BW(\text{kg}) \times 0.85}{72 \times S_{cr}}$$

S_{cr} = serum creatinine (mg/dL)
Actual body weight will be used for the CL_{cr}.

6.11.7. Pregnancy Testing

All females of childbearing potential will have a serum pregnancy test at Screening; FSH may be tested to determine a female subject's postmenopausal state (refer to Appendix 3). All females of childbearing potential will have a urine pregnancy test at Day 1 (prior to dosing) and every 4 weeks thereafter. In the event of a positive pregnancy result, subjects will be instructed to stop study drugs immediately (if applicable) and complete a serum pregnancy test.

CCI [redacted]

[redacted]

6.11.9. Health Related Quality of Life (HRQoL)

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.

6.11.9.1. Short Form 36 Health Survey (SF-36)

The SF-36 asks 36 questions to measure functional health and well-being from the subject's point of view. It consists of eight health domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. These health domain scales contribute to the physical health and mental health summary measures.

6.11.9.2. 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.

6.11.9.3. Work Productivity and Activity Impairment (WPAI)

The WPAI questionnaire asks questions regarding the effect of NASH on a person's ability to work and perform regular activities.

6.11.9.4. 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".

6.11.10. Pruritus Assessments

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.

6.11.10.1. Visual Analogue Scale- Itch (VAS-itch)

The VAS-itch is a tool for measuring the intensity of pruritus.

6.11.10.2. 5-D itch

The 5-D itch is multidimensional measure of itching that allows changes in chronic pruritus to be detected over time. The questionnaire measures the degree, duration, direction, disability, and distribution of pruritus.

6.11.11. Electrocardiogram

Standard 12-lead ECG assessments will be performed. 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.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

6.11.15. Liver Biopsy

All possible attempts should be made to acquire a liver biopsy specimen of at least 2.0 cm in length to ensure accurate staging of fibrosis and other histological lesions. It is recommended that a 16 gauge needle is used to collect the tissue sample. A historical biopsy within 6 months of the Screening visit (that is consistent with NASH and bridging fibrosis [F3]) or within 12 months of the Screening visit (that is consistent with NASH and cirrhosis (F4) or cirrhosis due to NASH with < 5% steatosis [F4, NAS steatosis grade = 0]) may be accepted as the Screening biopsy. The liver biopsy sample must be deemed adequate for evaluation by the central reader for inclusion.

Liver biopsies will be sent to a central laboratory and then read by a central reader. The central reader will read all Screening biopsies for eligibility. This assessment will include an assessment of the adequacy of the specimen as well as the fibrosis stage and a determination that the biopsy is consistent with NASH or cirrhosis due to NASH with < 5% steatosis. If liver biopsy results are deemed unevaluable by the central reader, a repeat biopsy may be performed at the discretion of the Investigator.

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

Please refer to the Site Operations Manual for additional information.

6.11.16. Lifestyle Modification Counseling

Lifestyle modifications such as weight loss via diet and increased exercise can be effective in the treatment of NASH. At each study visit, all subjects will receive counseling regarding lifestyle modifications including the maintenance of a healthy diet and participation in regular exercise.

6.11.17. Lifestyle Questionnaire

This questionnaire will assess the quantity of alcohol intake, dietary patterns, and physical activity of subjects before starting study drugs and between study visits.

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

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 post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. 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 eCRF.

7.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as an event that 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 were 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; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. 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 IMP 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 Section 7.2.2.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

The Investigator or qualified subinvestigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. 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 to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

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

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.

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 drugs, the following types of events should be reported on the eCRF: all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study drug, until 30 days after last administration of study drugs, all AEs regardless of cause or relationship, must be collected and 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 may request that certain AEs be followed beyond the protocol defined follow-up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur 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 post treatment follow-up period, must be reported to the eCRF database and Gilead 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 Follow-Up visit but within 30 days of the last dose of study drugs, 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 IMP, he/she should promptly document and report the event to Gilead PVE.

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:

  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.

Gilead Medical Monitor contact information is as follows:

Name: PPD
Telephone: PPD
Mobile: PPD
Fax: PPD
Email: PPD

7.4. Gilead Reporting Requirements

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

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

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

CCI [redacted]

[redacted]

[redacted]

[redacted]

7.5.2. Close Observation

Close observation includes:

- [redacted]
- 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.

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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.

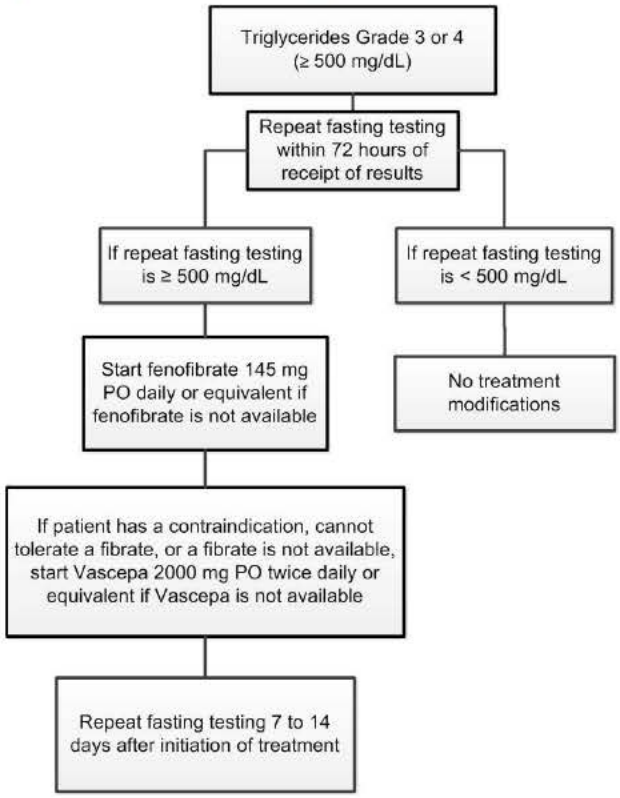
CCI [redacted]

[redacted]

7.5.4. 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



CCI [redacted]

[redacted]

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs associated with product complaints, occupational exposure with an AE, 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.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The Investigator should report pregnancies in female study subjects that are identified after initiation of study drugs and throughout the study, including the post study drug follow-up period, to Gilead PVE using the paper 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

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 Section 7.3. 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 or 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 or 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.

7.6.2.2. Reporting Other Special Situations

Site personnel must record all other special situations data in the eCRF database and from there transmit the special situations 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. All special situations data will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

If it is not possible to record and submit the special situations information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the information on the paper special situations report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to Gilead PVE. Gilead PVE contact information is as follows: Email: PPD and Fax: PPD

As soon as it is possible to do so, any special situations reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines. If any special situations have been reported via a paper form because the eCRF database has been locked, no further action is necessary.

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.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

Details will be provided in the statistical analysis plan (SAP).

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To assess the safety and tolerability of SEL, GS-0976, and GS-9674, administered alone or in combination, in subjects with bridging fibrosis or compensated cirrhosis due to NASH
- To evaluate changes in liver fibrosis, as measured by the NASH CRN classification, without worsening of NASH (defined as any increase in hepatocellular ballooning or lobular inflammation)

CCI

[redacted]

8.1.2. Endpoints

8.1.2.1. Primary Endpoint

The primary endpoints are the safety and anti-fibrotic effects of SEL, GS-0976, and GS-9674, administered alone or in combination, in subjects with bridging fibrosis or compensated cirrhosis due to NASH. Safety endpoints include AEs and laboratory evaluations.

Anti-fibrotic response will be evaluated by the proportion of subjects at Week 48 who achieve a ≥ 1-stage improvement in fibrosis (according to the NASH CRN classification) without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation).

[redacted]

[redacted]

8.2. Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using Statistical Analysis System (SAS®) software (SAS Institute, Cary, North Carolina, USA).

8.3. Analysis Sets

8.3.1. Efficacy

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

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

8.3.2. Safety

The primary analysis set for safety analyses will include all subjects who received at least one dose of study drugs. Subjects who received study drug other than that to which they were randomized for the entire duration of treatment will be analyzed according to the study drugs received.

All data collected during treatment plus 30 days after last dose of study drugs will be included in the safety summaries.

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[redacted]

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8.3.2.2. Biomarkers

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

8.4. Interim Analysis

An administrative interim analysis will be performed after all randomized subjects have completed Week 24 assessments or prematurely discontinued the study.

8.5. 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 drugs, the subject will be included in a summary of AEs 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 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.

Values for missing vital signs data will not be imputed; however, a missing baseline result will be replaced with a Screening result, if available.

Further details of data handling conventions and transformation will be provided in the SAP.

8.6. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data will include a summary of body weight, height, BMI, waist-to-hip ratio, randomization stratification groups (presence or absence of diabetes, fibrosis stage F3 or F4), and other disease characteristic variables.

8.7. Efficacy Analysis

8.7.1. Primary Efficacy Endpoints Analysis

The point estimates and 95% confidence intervals for the proportion of subjects who achieve a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 48 will be calculated by treatment group.

CCI [redacted]

8.8. Safety Analysis

All safety data collected on or after the date that study drugs were first dispensed up to the date of last dose of study drugs plus 30 days will be summarized by treatment group. Data for the pretreatment and follow-up periods will be included in data listings.

8.8.1. Extent of Exposure

Data of a subject's extent of exposure to study drugs will be generated from the study drugs administration eCRF data. Exposure data will be summarized by treatment group.

8.8.2. Adverse Events

Clinical and laboratory AEs 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. AE severity will be graded using the CTCAE.

Events will be summarized on the basis of the date of onset for the event. A TEAE will be defined as one or both of the following:

- Any AEs with an onset date on or after the study drugs start date and no later than 30 days after permanent discontinuation of study drugs
- Any AEs leading to premature discontinuation of study drugs

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

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

8.8.3. 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. Grading of laboratory abnormalities for analysis purposes will be defined in the Statistical Analysis Plan.

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 drugs 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.

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CCI [redacted]

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8.11. Sample Size

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof of concept studies; however, with a sample size of approximately 70 subjects in each active combination treatment arm and approximately 35 in the placebo arm, the study has over 80% power to detect a difference in the proportion of subjects with a $\geq$ 1-stage improvement in fibrosis without worsening of NASH of 25% or more at Week 48 at a significance level of 0.05 (two-sided), assuming the proportion of subjects that meet the endpoint in the placebo arm is 7.2%.

8.12. Data Monitoring Committee

An independent, external multidisciplinary data monitoring committee (DMC) that consists of at least two hepatologists and a statistician will review the progress of the study and perform interim reviews of safety data. The initial meeting of the DMC will occur after 35 subjects (approximately 5 per treatment group) have completed their Week 4 assessments and will meet at a minimum interval of every 6 months thereafter. The DMC will provide recommendations to Gilead 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 may also provide recommendations as needed regarding study design.

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

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

9. 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 Harmonisation (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. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/ Ethics Committee (EC) Review and Approval

The Investigator (or sponsor as appropriate according to local regulations) will submit this protocol, ICF, 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/IEC/EC. The Investigator will not begin any study subject activities until approval from the IRB/IEC/EC has been documented and provided as a letter to the Investigator.

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

9.1.3. 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 IRB/IEC/EC-approved consent form for documenting

written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC/EC local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only partial date of birth (as applicable in certain countries), another unique identifier (as allowed by local law), and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC/EC, 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 IB, this protocol, eCRFs, the IMP, 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.

9.1.5. 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/IEC/EC 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, PE, 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 drugs, including dates of dispensing and return
- Record of all AEs 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.

9.1.6. Electronic 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. eCRFs 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 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 captures 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 (eg, 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 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, study drugs should be destroyed at the site. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

The study monitor will provide instructions for return.

The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. 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 drugs are destroyed on site, the investigator must maintain accurate records for all study drugs 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. Refer to the Pharmacy Binder for study drug disposal/return instructions. The study monitor will review study drug supplies and associated records at periodic intervals.

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agencies. 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 9.1.4).

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 (eg, 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 authorities, IRBs, IECs, and ECs. 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.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib, GS-0976, GS-9674, and Combinations in Subjects with Bridging (F3) Fibrosis or Compensated Cirrhosis (F4) due to Nonalcoholic Steatohepatitis (NASH)

GS-US-454-4378, Amendment 4, 25 April 2019

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

PPD

PPD

PPD

4/25/2019

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

Assessments	Screening	Day 1	On-Treatment Visits													ET	Follow-Up
			Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48		
Clinical Assessments																	
Written Informed Consent	X																
Determine Eligibility	X	X															
Medical History	X																
Physical Examination	X[a]	X	X	X	X	X	X	X	X[a]	X	X	X	X	X	X[a]	X[a]	X
Vital Signs including Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																
CCI																	
12-lead ECG	X														X	X	X
CCI																	
Assess Ascites and HE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Abdominal Ultrasound	X[b]								X						X	X	
CCI																	
Liver Biopsy	X[e]														X	X[d]	
CCI																	

Assessments	Screening	Day 1	On-Treatment Visits													ET	Follow-Up
			Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48		
CCI																	
Lifestyle Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lifestyle Modification Counseling		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Study Drugs		X		X	X	X	X	X	X	X	X	X	X	X			
Review of Study Drug Dosing Compliance (Pill Count)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																	
Chemistry, Hematology, Coagulation	X	X[j]	X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin and Lipids	X	X		X		X			X			X			X	X	X
HbA1c	X[k]	X		X		X			X			X			X	X	X
eGFR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1, HBV, HCV Serology	X																
CCI																	

Assessments	Screening	Day 1	On-Treatment Visits													ET	Follow-Up
			Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48		
CCI																	
CCI																	
CCI																	
Pregnancy Testing[n]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																	
Urine Drug Screen	X																
Urine Collection (albumin, creatinine, albumin/creatinine ratio)		X				X			X			X			X	X	X
CCI																	
CCI																	
CCI																	

Assessments	Screening	Day 1	On-Treatment Visits												ET	Follow-Up
			Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48		
CCI																	

a Complete PE
b Historical ultrasound within 3 months inclusive to the date of Screening may be used
CCI
d At the discretion of the Investigator
e Historical liver biopsy (within 6 months of the Screening for F3 and within 12 months of the Screening for F4) may be accepted as the Screening biopsy
CCI
g To be completed upon confirmation of subject's eligibility; may be completed up to 7 days before or 3 days after Day 1
CCI
i AE reporting during Screening is limited to SAEs and AEs related to study procedures
j Additional testing: digoxin level at Day 1, Week 1, and as needed in subjects taking digoxin (refer to Section 5.3)
k If HbA1c is unable to be resulted, serum fructosamine will be tested
CCI
n For female subjects of childbearing potential only. Serum pregnancy test at Screening and urine pregnancy test at Day 1 and every 4 weeks thereafter, including ET. FSH may be tested at Screening to determine a female subject's postmenopausal state (refer to Appendix 3)
CCI

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 of 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

SEL is contraindicated in pregnancy as a malformation effect is suspected, based on non-clinical data. In rats and rabbits, SEL administration was associated with effects on embryo-fetal development at maternally toxic doses. This included total litter loss, increased resorptions and post implantation loss, reduced fetal weights, and visceral and skeletal malformations and variations. Embryofetal effects were observed in rats and rabbits at exposures (AUC_{24hr}) that were 62- and 12-fold higher, respectively, than the projected SEL exposure at the proposed human dose of 18 mg/day. The NOELs for embryofetal development in rats and rabbits were 15 and 10 mg/kg/day, respectively. The SEL exposure margins at these doses as compared to the maximum proposed human dose are 12- and 3-fold, respectively.

Preclinical data indicate that SEL is unlikely to reduce the exposure of hormonal contraceptives through induction of human drug metabolizing enzymes or drug transporters. This is supported by clinical DDI data, which demonstrated multiple doses of SEL did not result in exposure changes of a representative oral hormonal contraceptive, indicating no loss of contraceptive efficacy is expected upon administration of SEL with hormonal contraceptives.

No formal studies have been conducted to evaluate the reproductive toxicity of GS-0976; therefore, the reproductive toxicity of GS-0976 in humans is unknown. However, mutant mice lacking ACC1, one of the targets of GS-0976, are embryonically lethal. Therefore, GS-0976 is contraindicated in pregnancy.

Preclinical data in human hepatocytes indicate that GS-0976 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 GS-0976 with hormonal contraceptives. Please refer to Section 1.3.3.1 and the latest version of the Investigator's Brochure for additional information.

GS-9674 has not yet been studied in pregnant women. In 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 the 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 GS-9674. The NOEL for embryo/fetal 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 between GS-9674 and hormones used for contraception.

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

b) 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. Pregnancy tests will be performed at monthly intervals thereafter. Female subjects must agree to one of the following from Screening until 90 days 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 90 days after the last dose of study drug.

3) 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 90 days 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 90 days after the last dose of study drug.

4) 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.

5) 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 90 days 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 pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 4. West Haven Criteria

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

Grade of Hepatic Encephalopathy	Description	Suggested Operative Criteria
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/ behavioral decay with respect to his or her standard on clinical examination or to the caregivers
Grade II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least 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}