CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib in Subjects with Nonalcoholic Steatohepatitis (NASH) and Bridging (F3) Fibrosis
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	125393
EudraCT Number:	2016-004374-18
Clinical Trials.gov Identifier:	NCT03053050
Indication:	Nonalcoholic Steatohepatitis
Protocol ID:	GS-US-384-1943
Gilead Sciences Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD Email: PPD
Gilead Sciences Study Director:	Name: PPD Telephone: PPD Fax: PPD Email: PPD
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PROTOCOL SYNOPSIS

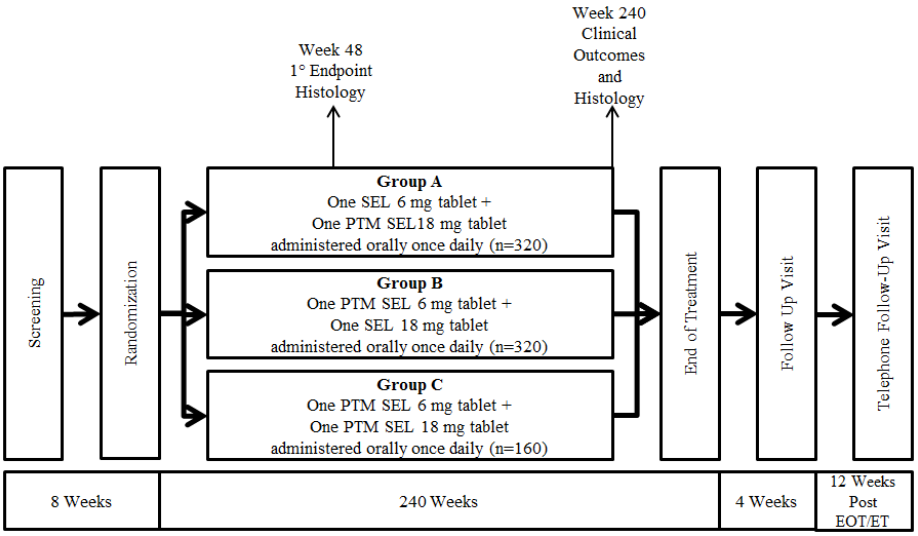
Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404 USA

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib in Subjects with Nonalcoholic Steatohepatitis (NASH) and Bridging (F3) Fibrosis
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	125393 2016-004374-18 NCT03053050
Study Centers Planned:	Approximately 460 centers globally
Number of Subjects Planned:	Approximately 800 subjects
Target Population:	Males and non-pregnant, non-lactating females between 18 - 70 years of age with NASH and bridging fibrosis.
Duration of Treatment:	Subjects will be treated for up to 240 weeks.
Duration of Study:	Individual subject participation in the study can last up to 260 weeks, which includes an 8-week Screening period, a 240-week treatment period, a 4-week Follow-Up period and a Telephone Follow-Up visit 12 weeks after the Week 240 or Early Termination (ET) visit, as applicable. The total study duration is anticipated to be approximately 7 years, including an enrollment period of approximately 2 years.
Objectives:	The primary objective of this study is: • To evaluate whether selonsertib (SEL, previously known as GS-4997) can cause fibrosis regression and reduce progression to cirrhosis and associated complications in subjects with NASH and bridging (F3) fibrosis The secondary objective of this study is: • To assess the safety and tolerability of SEL in subjects with NASH and bridging (F3) fibrosis

Study Design:

This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of SEL in subjects with NASH and bridging (F3) fibrosis.

Subjects meeting the study's entry criteria will be randomly assigned in a 2:2:1 ratio to 1 of 3 treatment groups 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 Screening lab values if previously undiagnosed [i.e. hemoglobin A1c (HbA1c) ≥ 6.5% or fasting plasma glucose ≥ 126 milligram/deciliter [mg/dL]) and by Enhanced Liver Fibrosis (ELF™) score ≥ 9.76 or < 9.76 during Screening. Study drugs will be administered for up to a total of 240 weeks.

A key primary objective of this study is to prevent progression to cirrhosis and its complications. A composite of clinical events that constitute the clinical efficacy endpoint have been identified and include:

1) Progression to cirrhosis as defined by a liver biopsy showing F4 fibrosis according to the NASH Clinical Research Network (CRN) classification as assessed by the central reader
2) Events of hepatic decompensation including:
   a) Clinically apparent ascites requiring treatment
   b) Hepatic encephalopathy (HE) of Grade 2 or above (according to the West Haven criteria as defined in Appendix 5) requiring treatment

c) 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

3) Liver transplantation or qualification for liver transplantation, defined as a Model for End-stage Liver Disease (MELD) score ≥ 15 on at least 2 consecutive occasions at least 4 weeks apart

4) All-cause mortality

Subjects who experience a confirmed hepatic clinical event prior to completing the Week 240 Visit of the Randomized Phase will be offered the option to rollover into an Open-Label (OL) Phase of the study. Each of the clinical events (except histologic progression to cirrhosis, all-cause mortality and liver transplantation) will require confirmation by a Hepatic Events Adjudication Committee. All deaths will be reviewed by this committee to determine if they are liver-related.

If a subject is clinically felt to have progressed to cirrhosis (e.g., based on the presence of new esophageal varices, changes in biomarkers [including, but not limited to, low serum albumin, high serum bilirubin, a low platelet count, prolonged INR, or elevated liver stiffness], or development of other clinical signs or symptoms of cirrhosis), the subject should undergo repeat liver biopsy for confirmation of progression to cirrhosis (F4 fibrosis as assessed by the central reader according to the NASH CRN classification) at the discretion of the primary investigator (PI).

Once the clinical event (except histologic progression to cirrhosis, all-cause mortality and liver transplantation) is confirmed by the Hepatic Events Adjudication Committee, the subject will no longer participate in the Randomized Phase and will be offered the option to receive SEL 18 mg in the OL Phase for a total treatment duration of 240 weeks inclusive of the Randomized Phase. Rollover into the OL Phase of the study must occur within 60 days of confirmation of the event. Subjects starting the OL Phase of the study will complete the same study procedures as during the Randomized Phase of the study, CCI [redacted]
Hepatic clinical events will be adjudicated and deaths will be reviewed by the Hepatic Events/DILI Adjudication Committee only during the Randomized Phase of the study; potential DILI events and cardiovascular events including deaths will continue to be adjudicated in the OL Phase by the Hepatic Events/DILI Adjudication Committee and the Cardiovascular Events Adjudication Committee, respectively.

Cardiovascular events including cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for cardiac failure, and coronary revascularization will be adjudicated by an independent Cardiovascular Events Adjudication Committee. Subjects experiencing a cardiovascular event will continue in the Randomized Phase and not rollover into the OL Phase. Cardiovascular events will be adjudicated during the Randomized Phase and the OL Phase of the study.

Diagnosis and Main Eligibility Criteria:

Key Inclusion Criteria

1) Liver biopsy consistent with NASH (defined as the presence of at least grade 1 steatosis, hepatocellular ballooning, and lobular inflammation according to the NAFLD Activity Score [NAS]) and bridging (F3 fibrosis) according to the NASH CRN classification, in the opinion of the central reader
   a) A historical liver biopsy within 6 months of the Screening visit may be accepted as the Screening biopsy if the sample is deemed acceptable for interpretation by the central reader
   b) If the subject is deemed ineligible for this study, the liver biopsy, if performed according to protocol specifications and is within 12 months of the Screening visit, may be used to determine eligibility for study GS-US-384-1944
2) Subject has the following laboratory parameters at the Screening visit, as determined by the central laboratory:
   a) Alanine aminotransferase (ALT) ≤ 8 x ULN
   b) Creatinine Clearance (CL_{cr}) ≥ 30 milliliter/minute (mL/min), as calculated by the Cockcroft-Gault equation
   c) HbA1c ≤ 9.5% (or serum fructosamine ≤ 381 µmol if HbA1c is unable to be resulted)
   d) Total bilirubin ≤ 1.3 x ULN (unless an alternate etiology such as Gilbert's syndrome or hemolytic anemia is present)
   e) INR ≤ 1.4, unless due to therapeutic anti-coagulation
   f) Platelet count ≥ 100,000/µL

Key Exclusion Criteria

1) Prior history of decompensated liver disease including ascites, HE, or variceal bleeding
2) CP score > 6, as determined at Screening, unless due to therapeutic anti-coagulation
3) MELD score > 12, as determined at Screening, unless due to therapeutic anti-coagulation

4) Chronic hepatitis B virus (HBV) infection (hepatitis B surface antigen [HBsAg] positive)
5) Chronic hepatitis C virus (HCV) infection (HCV Ab and HCV ribonucleic acid [HCV RNA] positive). Subjects cured of HCV infection less than 5 years prior to the Screening visit are not eligible
6) Other causes of liver disease including, but not limited to, alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders (e.g., primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis), drug-induced hepatotoxicity, Wilson disease, iron overload, and alpha-1-antitryspin deficiency, based on medical history and/or centralized review of liver histology
7) History of liver transplantation
8) Current or history of HCC
9) Any weight reduction surgery in the 2 years prior to Screening or planned during study (weight reduction surgery is disallowed during the study), and malabsorptive weight loss surgery (e.g., Roux-en-Y or distal gastric bypass) at any time prior to Screening
10) Weight loss > 10% within 6 months of Screening
11) Human immunodeficiency virus (HIV) infection
12) Unstable cardiovascular disease

Study Procedures/ Frequency:

Screening assessments will include complete medical history, physical exam (PE), vital signs, laboratory assessments, pregnancy tests (for females of child-bearing potential), liver biopsy (if required), standard 12-lead electrocardiogram (ECG), CCI [redacted] and review of adverse events (AEs) and concomitant medications.

Eligible subjects will be randomized to one of the three treatment groups: SEL 6 mg, SEL 18 mg or placebo to match (PTM). Prior to initial dosing, the following Day 1 assessments will be performed: symptom driven PE, vital signs, laboratory assessments, pregnancy tests (for females of child-bearing potential), liver stiffness measurement by elastography (if available), stool frequency assessment, Health Related Quality of Life (HRQoL) and Health Resource Utilization questionnaires, and review of AEs and concomitant medications.

After the Screening period and a 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 and every 12 weeks thereafter until Week 240 with a Follow-Up visit and a Telephone Follow-Up visit. At minimum, review of AEs and concomitant medications and safety laboratory tests will be performed at every visit.

CCI [redacted]

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

- Liver biopsy at Week 48 and Week 240 in the Randomized Phase only
- Abdominal ultrasound for HCC surveillance (OL Phase only prior to or on Day 1 and at Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240)
- Single PK sampling:
  - Randomized Phase at Weeks 1, 4, 12, 24, and 48 in all subjects
  - OL Phase, at all visits in subjects with severe hepatic impairment (Child-Pugh [CP] Class C) in combination with renal impairment (eGFR < 30 mL/min)
- Record subject's stool frequency
- Blood and urine for Biomarkers at Weeks 12, 24, 48, 96, 144, 192, and 240
- HbA1c at Weeks 4, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240
- Insulin and Lipids at Weeks 4, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240
- Symptom driven PE, vital signs, body weight, and lifestyle modification counseling
- Waist circumference at Weeks 4, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240
- HRQoL questionnaires: Short Form 36 [SF-36] Health Survey, Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease [CLDQ-NAFLD], Work Productivity and Activity Impairment [WPAI], EuroQol five dimensions [EQ-5D], and Health Resource Utilization questionnaire at Weeks 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240

	All subjects will complete the Follow Up visit and a Telephone Follow-Up visit. At the Follow Up visit, subjects will have a symptom driven PE, vital signs, review of concomitant medications and AEs, stool frequency assessment, and safety laboratory tests. A urine pregnancy test will be performed for females of childbearing potential only.
Test Product:	SEL 18 mg oral tablet once daily SEL 6 mg oral tablet once daily
Reference Therapy Dose:	PTM SEL 18 mg oral tablet once daily PTM SEL 6 mg oral tablet once daily
Dose, and Mode of Administration:	• Treatment Group A: one SEL 6 mg tablet + one PTM SEL 18 mg tablet administered orally once daily • Treatment Group B: one PTM SEL 6 mg tablet + one SEL 18 mg tablet administered orally once daily • Treatment Group C: one PTM SEL 6 mg tablet + one PTM SEL 18 mg tablet administered orally once daily
Criteria for Evaluation:	
Efficacy:	The primary efficacy endpoint at Week 48 includes the proportion of subjects 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). The clinical efficacy endpoint at Week 240 is event-free survival (EFS). EFS will be assessed by time to the first clinical event including progression to cirrhosis, liver decompensation events, liver transplantation, or all-cause mortality. Secondary Endpoints: • Proportion of subjects who have progression to cirrhosis by Week 48; • Proportion of subjects who have a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 240; • Proportion of subjects who have a ≥ 1-stage improvement in fibrosis at Week 48 and Week 240; • Proportion of subjects who have NASH resolution without worsening of fibrosis at Week 48 and Week 240

Safety:	The safety of SEL in subjects with bridging fibrosis due to NASH will be assessed during the study through the reporting of AEs, clinical laboratory tests, vital sign assessments and concomitant medication usage. An external Data Monitoring Committee (DMC) that consists of three hepatologists and a PhD statistician will review the progress of the study. They will convene after 50 subjects have completed the Week 4 visit and approximately every 6 months thereafter to monitor the study for safety events.
Statistical Methods:	**Primary Efficacy Endpoints Analysis:** A stratified Mantel-Haenszel (MH) test will be used to compare the differences in proportion of subjects who achieve a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 48 between each of the SEL arms and the placebo arm, adjusting for stratification factors. The point estimates and 95% confidence intervals for the differences in proportions will be calculated. **Clinical Endpoint Analysis:** The clinical efficacy endpoint at Week 240 is EFS. EFS will be assessed by time to the first clinical event in the Randomized Phase. Differences in time to the first clinical events between each of the SEL arms and the placebo arm will be assessed using the stratified log-rank test. The clinical efficacy endpoint will only be evaluated at Week 240 for the SEL arm if the SEL arm demonstrates superiority for the primary efficacy endpoint at Week 48. **Secondary Efficacy Endpoint Analyses:** A stratified MH test will be performed to compare the differences in proportions between each SEL arm and the placebo arm for the following endpoints: • Proportion of subjects who have progression to cirrhosis by Week 48; • Proportion of subjects who have a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 240; • Proportion of subjects who have a ≥ 1-stage improvement in fibrosis at Week 48 and Week 240; • Proportion of subjects who have NASH resolution without worsening of fibrosis at Week 48 and Week 240 **Assessment of Noninvasive Measures of Fibrosis:** Receiver operating characteristic (ROC) curves and measures of diagnostic test performance (e.g., sensitivity and specificity) will be used to determine whether baseline noninvasive measures of fibrosis and their change from baseline can predict histological regression and progression of fibrosis or the development of clinical complications.

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

Pharmacokinetic Analysis: Plasma concentrations of SEL and GS-607509 will be listed and summarized. CCI [redacted]

Sample Size: With a sample size of 320 subjects in each active treatment arm and 160 subjects in the placebo arm, the study has 94% power to detect a difference in the proportion of subjects with a ≥ 1-stage improvement in fibrosis without worsening of NASH of 15% or more at Week 48 at a significance level of 0.025 (two-sided), assuming the proportion of subjects that meet the endpoint in the placebo arm is 12%.

With regard to the clinical efficacy endpoint, subjects will be followed for a period of up to 240 weeks. The estimate of the expected event rate is 30% in untreated patients, producing an expected EFS rate of 70% at 240 weeks in the placebo arm. SEL is expected to improve the EFS rate to 83.7% (expected event rate of 16.3%) compared with placebo (hazard ratio (HR), 0.50). We also expect an overall dropout rate of 20%. Given the above assumptions, for comparison of each of the SEL arms versus the placebo arm, together with a total sample size of 800 subjects (2:2:1 ratio), and assuming the log-rank test statistic is evaluated using a two-sided 0.025 significance level, the study will have 85% power to evaluate the superiority of each SEL arm versus the placebo arm with respect to EFS.

Therefore, the overall power for the trial, assuming independence between the primary efficacy endpoint and clinical efficacy endpoint, is 80% (94% x 85%). It should be noted that this is a lower bound estimate because these two endpoints are expected to be positively correlated.

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

AE	adverse event
AH	alcoholic hepatitis
AICD	automatic implantable cardioverter defibrillator
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APTT	Activated Partial Thromboplastin Time
ASK1	apoptosis signal-regulating kinase 1
AST	aspartate aminotransferase
AUC	area under the curve
α-SMA	α-smooth muscle actin
BAP	Biomarker Analysis Plan
BCRP	Breast cancer resistance protein
BL	Baseline
BUN	blood urea nitrogen
CCR	Chemokine Receptor
CFR	Code of Federal Regulations
CI	confidence interval
c-Jun	c-Jun protein
CK18	Cytokeratin-18
CL_{cr}	creatinine clearance
CLDQ-NAFLD	Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease
C_{last}	last observed quantifiable plasma/serum concentration of the drug
C_{max}	maximum observed plasma/serum concentration of drug
CMH	Cochran-Mantel-Haenszel
CPK	Creatine phosphokinase
CP	Child-Pugh Score
CRF	Case Report Form
CRN	Clinical Research Network
CRO	contract (or clinical) research organization
CRP	c-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CXCL1	chemokine (C-X-C motif) ligand 1
CYP3A	cytochrome P4503A
CYP3A4	cytochrome P4503A4
DDI	drug-drug interaction

dL	deciliter
DILI	Drug-Induced Liver Injury
DKD	Diabetic Kidney Disease
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EFS	event-free survival
eGFR	estimated glomerular filtration rate
EDC	electronic data capture
e.g.	example
ELF™	enhanced liver fibrosis
EQ-5D	EuroQol five dimensions
EGD	Esophagogastroduodenoscopy
EU	European Union
EudraCT	European clinical trial database
F3	Bridging Fibrosis
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
FSH	Follicle stimulating Hormone
FXR	Farnesoid X Receptor
GCP	Good Clinical Practice
GI	Gastrointestinal
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
Hgb	Hemoglobin
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
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
HIV RNA	Human immunodeficiency virus ribonucleic acid

HLT	high-level term
HLGT	high-level group term
HOMA-IR	homeostatic assessment of insulin resistance
HPAH	Heritable pulmonary arterial hypertension
HR	hazard ratio
HRQoL	Health Related Quality of Life
IB	investigator's brochure
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IEC	independent ethics committee
IL-1β	interleukin 1b
IL-6	interleukin-6
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
JNK	c-Jun N-terminal kinase
kPa	kilopascal
LLT	lower-level term
MATE1	Multidrug and toxin extrusion protein 1
MCP-1	monocyte chemoattractant protein-1
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
µg	Microgram
Mg	Milligram
MH	Mantel-Haenszel
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
MQC	Morphometric quantitative collagen
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
n	number

NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
OATP	Organic anion-transporting polypeptide
OCT1	Organic cation transporter 1
OCT2	Organic cation transporter 2
OL	Open-Label
PAH	Pulmonary arterial hypertension
PD	Pharmacodynamic
PE	Physical exam
PK	Pharmacokinetic
P-gp	P-glycoprotein
p38	mitogen-activated protein kinase
p-p38	phospho-p38
PPAR	Peroxisome Proliferator-Activated Receptor
PRED	prednisolone
PT	Prothrombin time / Preferred Term
PTM	Placebo-to-Match
PVE	Pharmacovigilance and Epidemiology
PVR	pulmonary vascular resistance
Q	Every
QoL	Quality of Life
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
RBC	red blood cell count
RHC	right heart catheterization
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
SEL	Selonsertib
SD	standard deviation
SF-36	Short Form 36 Health Survey
SIM	Simtuzumab

SOC	System Organ Class
SOP	standard operating procedure
SREBP1c	sterol regulatory element binding protein-1c
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	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)
TEAEs	Treatment-emergent adverse events
TGF-β	Transforming growth factor beta
TIMP1	tissue inhibitor of metalloprotease 1
T_{last}	last measured concentration
T_{max}	time (observed time point) of C_{max}
TNF-α	tumor necrosis factor-alpha
UGT1A1	UDP glucuronosyltransferase family 1 member A1
ULN	upper limit of the normal range
US	United States
VAS	Visual Analog Scale
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 nonalcoholic fatty liver disease (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 (e.g., 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}.

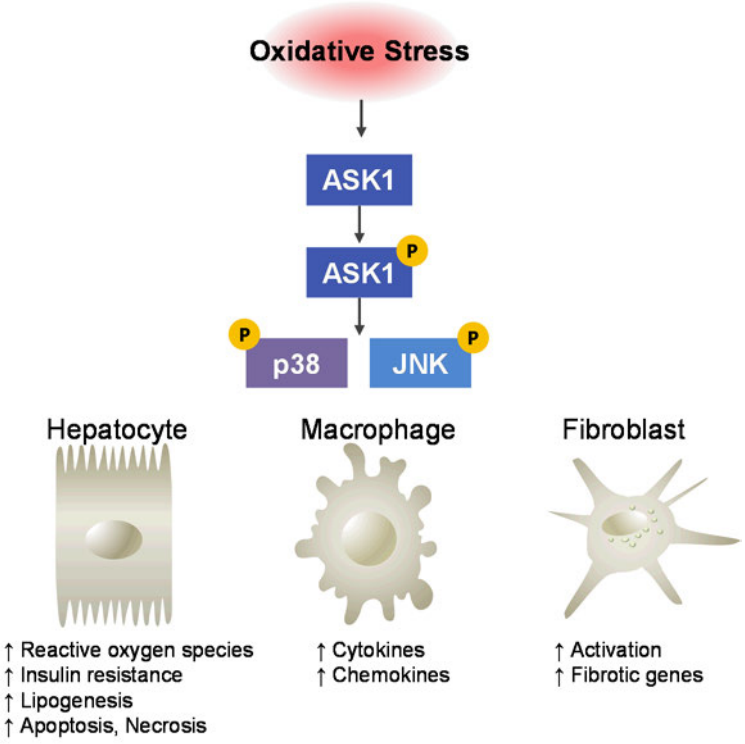
Over time, NASH may result in progressive liver fibrosis, ultimately resulting in cirrhosis. Advanced liver fibrosis (bridging fibrosis or cirrhosis) is associated with increased morbidity and mortality {Ekstedt 2014, Yeh 2014}. Cirrhosis increases the risk of developing hepatocellular carcinoma (HCC) 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. General Information for SEL

1.2.1. SEL

SEL is a potent and selective small molecule inhibitor of apoptosis signal-regulating kinase 1 (ASK1). ASK1 is an 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 (JNK) kinases. 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.

- In hepatocytes, JNK and p38 signaling induces metabolic dysfunction that promotes lipid accumulation and hepatic steatosis. JNK serine phosphorylates the insulin receptor substrate 1 (IRS1) promoting hepatic insulin resistance {Imoto 2006, Vallerie 2010}. Additionally, JNK phosphorylates and activates the liver X receptor (LXR) to increase transcription of sterol regulatory element binding protein-1c (SREBP1c) {Kim 2010}. SREBP1c is a core regulator of hepatic lipid metabolism that increases de novo lipogenesis and promotes hepatic steatosis. Additionally, p38 and JNK directly phosphorylate SREBP1c and SREBP1a to promote lipogenesis in the liver {Knebel 2014, Kotzka 2012}. In a mouse model of NASH, ASK1 inhibition reduced SREPB1c RNA expression and hepatic steatosis.
- Sustained p38 and JNK activation in hepatocytes induces mitochondrial dysfunction, ROS production and cell death by apoptosis or necrosis. JNK signaling at the mitochondria inhibits respiration and increases ROS production, leading to a feed forward cycle of sustained ASK1 and JNK activation and oxidative stress{Win 2016, Xie 2015}. p38 and JNK phosphorylate BCL-2 family members to promote hepatocyte apoptosis or necrosis, both of which exacerbate hepatic inflammation and fibrosis in NASH {Canbay 2004, Ichijo 1997, Kaufmann 2009, Nakagawa 2008, Wissing 2014}. In liver injury models, ASK1 inhibition reduced hepatocyte apoptosis and necrosis {Nakagawa 2011, Nakagawa 2008, Xie 2015}.
- p38 and JNK signaling in macrophages and other immune cells promote hepatic inflammation. JNK is required for polarization of macrophages to a pro-inflammatory state {Han 2013, Sabio 2014}. In addition, p38 phosphorylates AP1 transcription factors including ATF4, promoting the expression and secretion of inflammatory cytokines {Arthur 2013, Sabio 2014}. In mouse models of NAFLD and liver fibrosis, p38 and JNK promote expression of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 1b (IL-1β) and interleukin-6 (IL-6), chemokines such as monocyte chemoattractant protein-1 (MCP-1) and chemokine C-X-C motif ligand 1(CXCL1), and profibrotic mediators such as TGFβ {Gonzalez-Teran 2016, Vallerie 2010}. In rodent models of NASH, ASK1 inhibition reduced hepatic inflammation and the hepatic RNA expression of TNFα and MCP1.
- In NASH, hepatic stellate cells differentiate into myofibroblasts, which are a primary source of collagen and extracellular matrix production. JNK signaling is required for differentiation of hepatic stellate cells into myofibroblasts in vitro and in mice {Kluwe 2010}. p38 signaling in myofibroblasts promotes the transcription of collagen 1 and increases the expression of tissue inhibitor of metalloprotease 1 (TIMP1) to inhibit digestion and turnover of extracellular matrix by metalloproteases {Nieto 2006}. In a rodent model of NASH, ASK1 inhibition led to decreased phospho-p38 (p-p38) expression in fibroblasts and decreased RNA levels of collagen 1 and TIMP1. In vitro, SEL inhibited JNK phosphorylation and fibroblast activation in response to TGF-β2 stimulation.

- 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.

For further information on SEL, refer to the Investigator's Brochure (IB).

1.2.2. Preclinical Pharmacology and Toxicology

SEL has high oral bioavailability, moderate volume of distribution and low systemic clearance in nonclinical species and humans. SEL is modestly bound in human plasma. Elimination of SEL and its metabolites is likely to occur through a mixture of urinary, biliary and intestinal excretion. The main route of metabolism of SEL involves N-dealkylation. Human metabolism appears to be largely catalyzed by cytochrome P4503A (CYP3A) enzymes. After oral dosing of SEL significant concentrations of GS-607509, inactive N-dealkylation metabolite, are found in plasma. SEL is an inhibitor of CYP3A and UDP glucuronosyltransferase family 1 member A1 (UGT1A1) enzymes; however, clinically relevant inhibition of CYP3A was not observed in humans. SEL is a weak inhibitor of the transporters breast cancer resistance protein (BCRP), OATP1B1, and OATP1B3 and a more potent inhibitor of P-glycoprotein (P-gp), Organic cation transporter 1 (OCT1), Organic cation transporter 2 (OCT2), and Multidrug and toxin extrusion protein 1 (MATE1). The metabolite GS-607509 did not inhibit any of the CYP enzymes and was a very weak inhibitor of UGT1A1. GS-607509 shows little inhibition of all tested transporters apart from MATE1.

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), GI tract (profuse diarrhea) and kidney (tubular basophilia, eosinophilic droplets, and pigment), embryofetal effects (visceral and/or skeletal malformations) and occurred at exposures that were in excess of the targeted human exposure at 18 mg/day. Similar findings have not been observed to date in clinical studies of SEL at doses of up to 100 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 16 February 2018, 15 Phase 1 and 2 clinical studies have been conducted/are ongoing in which 390 healthy subjects, 248 subjects with diabetic kidney disease (DKD), 145 subjects with pulmonary arterial hypertension (PAH), 50 subjects with alcoholic hepatitis (AH), and 122 subjects with NASH have been dosed with SEL. In addition, as of 12 January 2018, approximately 865 subjects with NASH have been dosed with SEL in this Phase 3 study and the Phase 3 GS-US-384-1944 study which are evaluating SEL in patients with advanced fibrosis due to NASH (treatment assignment remains blinded).

Information on the Phase 1 clinical studies and additional details on the Phase 2 and 3 studies can be found in the IB.

1.2.4. A Phase 2, Double-blind, Placebo-controlled, Dose-ranging Study Evaluating the Efficacy, Safety, and Tolerability of Selonsertib in Subjects with Diabetic Kidney Disease (Study GS-US-223-1015)

Study GS-US-223-1015 is a Phase 2, double-blind, placebo-controlled, dose-ranging study that evaluated the efficacy, safety, and tolerability of SEL in subjects with DKD. Three-hundred and thirty-three subjects with type 2 diabetes mellitus and Stage 3 or Stage 4 renal impairment and albuminuria receiving standard of care treatment for DKD were randomized (1:1:1:1) to 1 of 4 treatment groups: SEL 2, 6, or 18 mg or matching placebo administered once daily for 48 weeks. The primary objective of this study was to determine the effect of SEL on the decline of estimated glomerular filtration rate (eGFR) in subjects with DKD.

1.2.4.1. Subject Disposition

Of the 334 randomized subjects, 333 subjects were treated with placebo or study drug: 85 subjects with placebo and 248 subjects with active treatment (81, 84, and 83 subjects with SEL 2, 6, and 18 mg, respectively).

A total of 256 subjects (76.9%) completed treatment and 76 subjects (22.8%) discontinued study drug (19 subjects [22.4%] in the placebo group and 57 subjects [23.0%] in the pooled active treatment group [18.5%, 21.4%, and 28.9% for SEL 2, 6, and 18 mg, respectively]). The most frequent reason for discontinuation of study drug was due to an AE (4 subjects [4.7%] in the placebo group and 18 subjects [7.3%] in the pooled active treatment group), followed by progression to end-stage renal disease (4 subjects [4.7%] in the placebo group and 13 subjects [5.2%] in the pooled active treatment group), and withdrawal of consent (3 subjects [3.5%] in the placebo group and 13 subjects [5.2%] in the pooled active treatment group).

1.2.4.2. Safety Analyses

Overall 80.8% of subjects had a treatment-emergent adverse event with a frequency of 83.5% in the placebo group and 79.8% in the pooled active group (79%, 84.5%, and 75.9% for 2 mg, 6 mg and 18 mg, respectively). Adverse events related to study drug occurred in 9.4% of subjects in the placebo group and 12.5% of subjects in the pooled active treatment group (8.6%, 11.9%, and 16.9% for 2 mg, 6 mg and 18 mg, respectively). Overall, deaths occurred in 1.2% of subjects with a frequency of 1.2% in the placebo group and 1.2% in the pooled active treatment group (1.2%, 1.2%, and 1.2% for 2 mg, 6 mg and 18 mg, respectively). SEL treatment was well tolerated and no dose-limiting toxicity was observed.

1.2.4.3. Efficacy Analyses

The primary endpoint measure of eGFR change from baseline at Week 48 was -3.20 (SE 0.85), -2.83 (0.86), -2.37 (0.87), and -4.07 (0.89) mL/min/1.73 m^2 for placebo, 2 mg, 6 mg and 18 mg SEL respectively (p= NS). The study did not demonstrate that SEL lead to a statistically significant decrease in eGFR after 48 weeks of treatment compared to placebo.

1.2.5. A Phase 2, Dose-ranging, Randomized, Double-blind, Placebo-controlled Study of Selonsertib in Subjects with Pulmonary Arterial Hypertension (Study GS-US-357-1394)

Study GS-US-357-1394 is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study of SEL in subjects with PAH receiving background stable PAH therapy. One-hundred and fifty-one subjects with a diagnosis of idiopathic PAH (IPAH), heritable PAH (HPAH), or PAH associated with connective tissue disease (PAH-CTD), congenital heart defects (repaired), drug and toxin use, or HIV infection were randomized 1:1:1:1 to receive either SEL 2, 6, or 18 mg or placebo, orally, once daily, for 24 weeks (Period 1). Subjects continued to receive their background PAH therapy throughout the study. Subjects who completed the 24-week blinded treatment period were eligible to continue (or initiate) treatment with SEL at 2, 6, or 18 mg during the blinded, long-term treatment extension of this study (Period 2). The Active Period was defined for individuals who received at least 1 SEL dose, including subjects who received SEL in Period 2 only. The primary objective of this study was to evaluate the effect of SEL on pulmonary vascular resistance (PVR), as measured by right heart catheterization (RHC) in subjects with PAH.

1.2.5.1. Subject Disposition

Of the 151 randomized subjects, 150 subjects were treated with placebo or study drug in Period 1: 37 subjects with placebo and 113 subjects with active treatment (39, 37, and 37 subjects with SEL 2, 6, and 18 mg, respectively). A total of 129 subjects (97 from the SEL groups and 32 from the placebo group) continued into Period 2 of the study. All subjects discontinued study drug during Period 2, primarily because the sponsor terminated the study (82.9% of subjects overall).

A total of 132 subjects (88.0%) completed Period 1 treatment and 18 subjects (12.0%) discontinued study drug before reaching Week 24 (5 subjects [13.5%] in the placebo group and 13 subjects [11.5%] in the pooled active treatment group [12.8%, 16.2%, and 5.4% for SEL 2, 6, and 18 mg, respectively]). The most frequent reason for discontinuation of study drug was due to an AE (2 subjects [5.4%] in the placebo group and 6 subjects [5.3%] in the pooled active treatment group), followed by investigator's discretion (0 subjects in the placebo group and 3 subjects [2.7%] in the pooled SEL group), death (1 subject [2.7%] in the placebo group and 2 subjects [1.8%] in the pooled active treatment group), and increase in dose of PAH medication or new PAH medication added (1 subject [2.7%] in the placebo group and 2 subjects [1.8%] in the pooled SEL group).

1.2.5.2. Safety Analyses

In Period 1, AEs were reported with a frequency of 97.3% in the placebo group and 90.3% in the pooled active group (89.7%, 91.9%, and 89.2% for 2 mg, 6 mg and 18 mg, respectively). Adverse events related to study drug occurred in 48.6% in placebo and 42.5% in the pooled active treatment group (25.6%, 56.8%, and 45.9% for 2 mg, 6 mg and 18 mg, respectively). In the Active Period, AEs were reported for 98.0%, 93.9%, and 97.9% of subjects in the SEL 2, 6, and 18 mg groups, respectively. In both Period 1 and the Active Period, the most commonly reported AEs were headache, diarrhea, and nausea.

Over the course of the study and during follow-up vital status checks, a total of 12 subjects died (3, 5, and 2 subjects in the SEL 2, 6, and 18 mg groups, respectively, and 2 subjects in the placebo group). Nine of the deaths (7 subjects who received SEL and 2 subjects who received placebo only) were treatment emergent. Of the treatment-emergent deaths, 6 occurred during Period 1 and 3 occurred during the Active Period (after Period 1).

There were no dose-related trends in AE reporting across the SEL doses evaluated.

1.2.5.3. Efficacy Analyses

The primary efficacy endpoint (change in PVR from baseline to Week 24) and secondary efficacy endpoints were not met.

1.2.6. Study GS-US-416-2124: A Phase 2, Double-Blind, Randomized Study Evaluating the Safety, Tolerability, and Efficacy of SEL in Combination with Prednisolone versus Prednisolone Alone in Subjects with Severe Alcoholic Hepatitis

1.2.6.1. Study Design

Study GS-US-416-2124 is an ongoing Phase 2, double-blind, randomized study evaluating the safety, tolerability, and efficacy of SEL in combination with prednisolone (PRED) versus PRED alone in subjects with severe, histologically-confirmed AH. The study is fully enrolled. Subjects were required to have a clinical diagnosis of severe AH (Maddrey's discriminant function [DF] ≥ 32) based on a history of excessive alcohol consumption (> 40 g/day for women; > 50 g/day for men) and onset of jaundice during the past 3 months, AST ≥ 50 and ≤ 400 U/L, ALT ≤ 300 U/L, and AST/ALT ratio ≥ 1.5. Model for End-Stage Liver Disease (MELD) score was to be ≤ 30 and Maddrey's DF ≤ 60 at screening. Up to 120 subjects were to be randomized in a 1:1 ratio to 1 of 2 treatment groups: SEL 18 mg once daily + PRED 40 mg once daily for 28 days (Group A) or SEL placebo once daily + PRED 40 mg once daily for 28 days (Group B). Subjects will be followed for an additional 20-week posttreatment period. The primary endpoint is the safety of SEL in combination with PRED versus PRED alone.

Preliminary safety data from the primary analysis, based on a data cutoff date of 16 February 2018 (date of the Week 8 visit for the last subject), are presented below.

1.2.6.2. Subject Disposition

As of 16 February 2018, a total of 104 subjects were randomized (52 in each group). Of the randomized subjects, 102 received at least 1 dose of study drug (50 and 52 in the SEL + PRED and placebo + PRED groups, respectively). A total of 77 subjects (75.5% overall) completed treatment with SEL or placebo; 18 subjects (36.0%) discontinued SEL and 7 subjects (13.5%) discontinued placebo treatment in the SEL + PRED and placebo + PRED groups, respectively. The reasons for discontinuation of SEL were AE (14.0%), lack of efficacy (12.0% met protocol stopping criteria and 4.0% at investigator's discretion), and subject or proxy decision, death, and liver biopsy inconsistent with diagnosis of severe AH (each 2.0%). In the placebo + PRED

group, the reasons for discontinuation of placebo were AE (7.7%), subject or proxy decision (3.8%), and protocol violation (1.9%). Thirty subjects (60.0%) in the SEL + PRED group and 40 subjects (76.9%) in the placebo + PRED group completed treatment with PRED.

As of 16 February 2018, 16 subjects (32.0%) in the SEL + PRED and 23 subjects (44.2%) in the placebo + PRED groups remain on study in the posttreatment follow-up period.

1.2.6.3. Safety Results

The frequency of AEs was similar for both treatment groups: 47 subjects (94.0%) and 49 subjects (94.2%) in the SEL + PRED and placebo + PRED groups, respectively. The frequency of treatment-related AEs was similar for both groups: 13 subjects (26.0%) and 14 subjects (26.9%) in the SEL + PRED and placebo + PRED groups, respectively. Adverse events leading to discontinuation of SEL or placebo were reported for 9 subjects (18.0%) in the SEL + PRED group and 4 subjects (7.7%) in the placebo + PRED group.

At the time of the data cutoff date of 16 February 2018, a total of 20 subjects had died: 14 subjects (28.0%) in the SEL + PRED group and 6 subjects (11.5%) in the placebo + PRED group. The majority of these deaths occurred after subjects had completed or prematurely discontinued study drug. Four deaths (2 in each group) occurred up to Day 28 (i.e., during the planned duration of treatment). Most deaths involved complications of severe alcoholic hepatitis, including infections.

The most commonly reported AEs in the SEL + PRED group were ascites and hyponatremia (each 16 subjects [32.0%]), hepatic encephalopathy (14 subjects [28.0%]), and edema peripheral (13 subjects [26.0%]). In the placebo + PRED group, the most commonly reported AEs were ascites (15 subjects [28.8%]), edema peripheral (11 subjects [21.2%]), and hepatic encephalopathy (10 subjects [19.2%]).

A greater percentage of subjects in the SEL + PRED group (25 subjects [50.0%]) experienced SAEs compared with the placebo + PRED group (21 subjects [40.4%]). The most common SAEs overall were hepatic encephalopathy, acute kidney injury, cellulitis, coagulopathy, hepatorenal syndrome, hyponatremia, and pneumonia. A greater percentage of subjects in the SEL + PRED group (12 subjects [24.0%]) experienced SAEs of infections compared with the placebo + PRED group (5 subjects [9.6%]), which included SAEs of brain abscess reported in 2 subjects in the SEL + PRED group at the same study site (PTs: brain abscess and fungal abscess central nervous system, 1 subject each).

Overall, rates of AEs were similar between subjects in the SEL + PRED and placebo + PRED groups. However, higher rates of serious infections and hyponatremia were seen in subjects with severe AH who received SEL + PRED compared with placebo + PRED.

1.2.7. 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) (GS-US-384-1497)

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 LOXL2 evaluated for the treatment of NASH) for 24 weeks in subjects with NASH and fibrosis stages F2 or F3.

The primary objective of this study was to evaluate the safety and tolerability of SEL alone or in combination with SIM in subjects with NASH and fibrosis stages F2 or F3. Subjects were randomized in a 2:2:1:1:1 ratio to 1 of 5 treatment groups:

- SEL 6 mg orally once daily (N = 20)
- SEL 18 mg orally once daily (N = 22)
- SEL 6 mg orally once daily + SIM 125 mg subcutaneous injection weekly (N = 10)
- SEL 18 mg orally once daily + SIM 125 mg subcutaneous injection weekly (N = 10)
- SIM 125 mg subcutaneous injection weekly (N = 10)

Randomization was stratified by the presence or absence of diabetes mellitus as determined by medical history or based on screening laboratory values if previously undiagnosed (i.e., hemoglobin A1c [HbA1c] ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dL).

Overall, after 24 weeks of treatment, no additional benefit was observed with the addition of SIM 125 mg to the SEL (18 or 6 mg) study treatment regimens. Moreover, data from the SIM Phase 2b program (studies GS-US-321-0105 and GS-US-321-0106) showed that SIM has no anti-fibrotic effect in subjects with advanced fibrosis due to NASH. Therefore, preliminary efficacy results are presented by the following pooled groups: SEL 18 mg ± SIM 125 mg, SEL 6 mg ± SIM 125 mg, and SIM 125 mg alone.

1.2.7.1. Subject Disposition and Demographics

A total of 72 subjects were randomized and treated across 23 sites (21 in the US and 2 in Canada); 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.

1.2.7.2. Safety Results

Overall, 79.2% of subjects had a treatment-emergent adverse event with a frequency of 70% in the SIM alone group and 80.6% in the pooled active group (85%, 68.2%, 90%, and 90% in the SEL 6 mg, SEL 18 mg, SEL 6 mg + SIM, and SEL 18 mg + SIM, respectively). Adverse events related to study drug occurred in 0% of the SIM alone group and 33.9% in the pooled active treatment group (40%, 31.8%, 20%, and 40% in the SEL 6 mg, SEL 18 mg, SEL 6 mg + SIM, and SEL 18 mg + SIM, respectively).

Overall, SEL 6 mg or 18 mg ± SIM 125 mg administered for 24 weeks was generally well tolerated in study GS-US-384-1497. The majority of subjects reported at least 1 AE, and most AEs were mild or moderate in severity. Three subjects discontinued study treatment due to AEs: 2 subjects (9.1%) in the SEL 18 mg group (diarrhea and hypoesthesia in 1 subject and increased hepatic enzymes in 1 subject) and 1 subject (5.0%) in the SEL 6 mg group (worsened schizophrenia). A total of 11 SAEs were reported in 5 subjects during the study. Of these, only 1 SAE (hypoesthesia) was considered related to study drug by the investigator. No trends in SAE type or onset were observed. There were no deaths reported. Treatment-emergent Grade 3 and 4 laboratory abnormalities were infrequent. There were 4 subjects who developed an increase of ALT or AST of at least 2 × baseline and at least 3 × ULN, leading to permanent discontinuation of study drug in 1 subject. No trends in ECG findings suggestive of cardiac abnormalities were observed.

1.2.7.3. Efficacy Results

1.2.7.3.1. Histology

1.2.7.3.1.1. Change in Liver Fibrosis including NASH CRN Fibrosis Stage and Hepatic Collagen Content

Table 1-1 presents a summary of selected histologic endpoints following 24 weeks of treatment with SEL 18 mg ± SIM 125 mg, SEL 6 mg ± SIM 125 mg, or SIM 125 mg alone. Figure 1-2 presents fibrosis response for subjects with evaluable NASH CRN fibrosis stage data at Week 24.

At Week 24, there were more subjects with fibrosis improvement (≥ 1 stage decrease in NASH CRN fibrosis stage from baseline) in the SEL 18 mg ± SIM 125 mg group (43.3%, 13 of 30 subjects) and in the SEL 6 mg ± SIM 125 mg group (29.6%, 8 of 27 subjects) compared with the SIM 125 mg alone group (20.0%, 2 of 10 subjects). The proportion of SEL treated subjects with fibrosis improvement was greater in those with baseline F3 fibrosis (50.0%, 10 of 20 subjects in the SEL 18 mg ± SIM 125 mg group and 35%, 7 of 20 subjects in the SEL 6 mg ± SIM 125 mg group) compared to those with baseline F2 fibrosis (30%, 3 of 10 subjects in the SEL 18 mg ± SIM 125 mg group and 14.3%, 1 of 7 in the SEL 6 mg ± SIM 125 mg group).

No additional benefit was observed with the addition of SIM 125 mg to the SEL (18 or 6 mg) study treatment regimens. At Week 24, the number of subjects with fibrosis improvement without worsening of NASH inflammation or ballooning was 42.9% (9 of 21 subjects) in the

SEL 18 mg alone group and 23.5% (4 of 17 subjects) in the SEL 6 mg alone group compared with the SEL 18 mg + SIM group (11.1%, 1 of 9 subjects) and the SEL 6 mg + SIM group (30%, 3 of 10 subjects).

Fewer subjects had worsening in the NASH CRN fibrosis stage at Week 24 or progressed to cirrhosis in the SEL 18 mg ± SIM 125 mg group (6.7%, 2 of 30 subjects or 3.3%, 1 of 30 subjects, respectively) and the SEL 6 mg ± SIM 125 mg group (14.8%, 4 of 27 subjects or 7.4%, 2 of 27 subjects, respectively) compared with the SIM 125 mg alone group (40.0%, 4 of 10 subjects or 20.0%, 2 of 10 subjects, respectively).

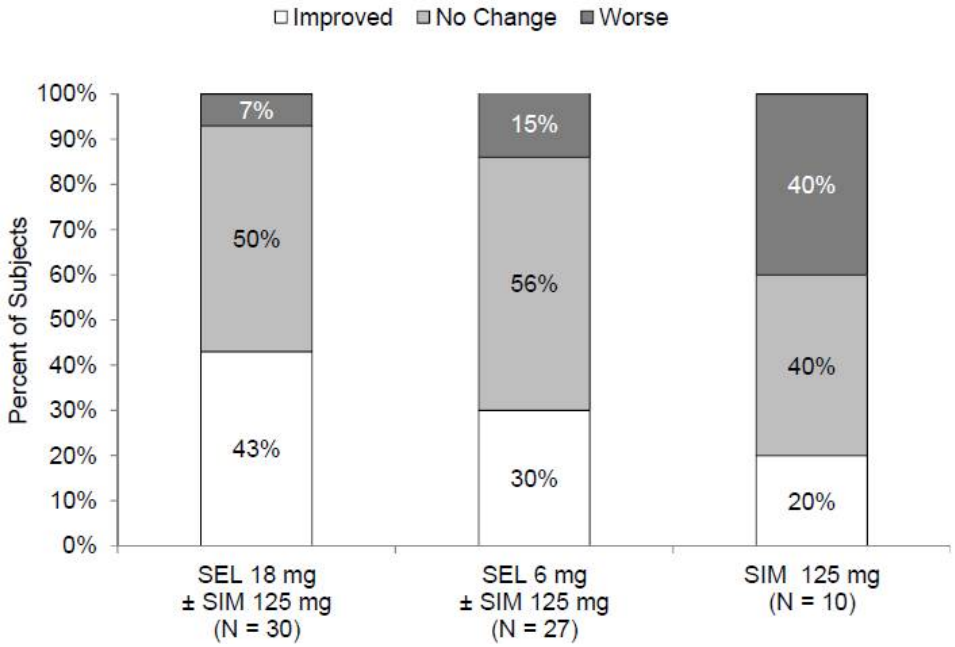
Table 1-1. GS-US-384-1497: Selected Histologic Endpoints at Week 24 (Evaluable Subjects, Full Analysis Set)

	SEL 18 mg ± SIM 125 mg (N = 32)	SEL 6 mg ± SIM 125 mg (N = 30)	SIM 125 mg (N = 10)
Subjects with Fibrosis Improvement at Week 24	13/30 (43.3%)	8/27 (29.6%)	2/10 (20.0%)
95% CI	25.5% to 62.6%	13.8% to 50.2%	2.5% to 55.6%
Subjects with Fibrosis Improvement without Worsening in NASH inflammation or ballooning at Week 24	10/30 (33.3%)	7/27 (25.9%)	2/10 (20.0%)
95% CI	17.3% to 52.8%	11.1% to 46.3%	2.5% to 55.6%
Subjects with Worsening of Fibrosis at Week 24	2/30 (6.7%)	4/27 (14.8%)	4/10 (40.0%)
95% CI	0.8% to 22.1%	4.2% to 33.7%	12.2% to 73.8%
Subjects with Progression to Cirrhosis at Week 24	1/30 (3.3%)	2/27 (7.4%)	2/10 (20.0%)
95% CI	0.1% to 17.2%	0.9% to 24.3%	2.5% to 55.6%
Subjects with NAS Response at Week 24	7/31 (22.6%)	5/27 (18.5%)	2/10 (20.0%)
95% CI	9.6% to 41.1%	6.3% to 38.1%	2.5% to 55.6%
Subjects with NAS Response and without Worsening of Fibrosis at Week 24	7/31 (22.6%)	5/27 (18.5%)	1/10 (10.0%)
95% CI	9.6% to 41.1%	6.3% to 38.1%	0.3% to 44.5%

Fibrosis improvement was defined as at least 1-stage decrease in NASH CRN fibrosis stage from baseline at Week 24.
No worsening was defined as postbaseline - baseline ≤ 0.
Progression to cirrhosis was defined as NASH CRN fibrosis stage increase to 4 from 2 or 3 at baseline.
NAS Response was defined as NAS decrease by 2 or more from baseline.
Within-group CI was based on Clopper-Pearson method.

Median percent change from baseline at Week 24 in morphometric collagen content for subjects treated with SEL 18 mg ± SIM 125 mg or SEL 6 mg ± SIM 125 mg were −8.7% and −8.2%, respectively, compared with an increase of 2.1% in subjects treated with SIM 125 mg alone.

Figure 1-2. GS-US-384-1497: NASH CRN Fibrosis Response at Week 24 (Evaluable Subjects, Full Analysis Set)



Fibrosis improvement was defined as ≥ 1-stage decrease in NASH CRN fibrosis stage from baseline at Week 24.
Fibrosis worsening was defined as ≥1-stage increase in NASH CRN fibrosis stage from baseline at Week 24.

1.2.7.3.1.2. Change in NAFLD Activity Score (NAS)

There were improvements (≥ 1 point) in the NAS for subjects in the SEL 18 mg ± SIM 125 mg group (51.6%, 16 of 31 subjects), the SEL 6 mg ± SIM 125 mg group (40.7%, 11 of 27 subjects), and the SIM 125 mg alone group (60.0%, 6 of 10 subjects). Improvements in the NAS resulted from improvements in all 3 subscores of steatosis, lobular inflammation, and hepatocyte ballooning, without a clear predominance of improvement in any single subscore. There was a greater proportion of subjects in the SEL 18 mg ± SIM 125 mg group (32.3%, 10 of 31 subjects) and the SEL 6 mg ± SIM 125 mg group (22.2%, 6 of 27 subjects), that achieved a ≥ 1-point improvement in the lobular inflammation subscore than in the SIM 125 mg alone group (20.0%, 2 of 10 subjects). Fewer subjects in the SEL 18 mg ± SIM 125 mg group (9.7%, 3 of 31 subjects) and the SEL 6 mg ± SIM 125 mg group (18.5%, 5 of 27 subjects) had worsening in the NAS compared with the SIM 125 mg alone group (30.0%, 3 of 10 subjects).

1.2.7.3.1.3. Change in Cytokeratin-18

Cytokeratin-18 (CK18) is an intracellular protein expressed at high levels in most cell types of epithelial origin, including hepatocytes, which can be used as a marker of hepatocyte death. The CK18 M30 subfraction represents a caspase cleavage product that indicates apoptotic cell death, while CK18 M65 indicates total soluble CK18 released from dead (apoptotic and necrotic) hepatocytes {Feldstein 2009}. Across all groups, decreases from baseline in CK18 M30 and CK18 M65 fractions were observed at Week 24. Greater median relative decreases in CK18 M30

and M65 were observed in the SEL 18 mg ± SIM 125 mg group (−31% and −44%, respectively) and the SEL 6 mg ± SIM 125 mg group (−6% and −35%, respectively) compared with the SIM 125 mg alone group (22% and −4%, respectively).

1.2.7.3.1.4. 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 MQC (−8.7% and −8.2%, respectively) versus an increase of 2.1% in subjects treated with SIM 125 mg alone

- Greater reductions in CK18 M30 and 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.

1.2.8. Study GS-US-384-3914: A Phase 2, Proof-of-Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Regimens in Subjects with Nonalcoholic Steatohepatitis

1.2.8.1. Study Design

Study GS-US-384-3914 is an ongoing Phase 2, proof-of-concept, open-label study evaluating the safety, tolerability, and efficacy of SEL, GS-0976, and GS-9674 in subjects with NASH as assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE). Cohorts 1 through 6 and 9 will evaluate treatments in noncirrhotic subjects and Cohorts 7 and 8 will evaluate treatments in cirrhotic subjects.

A total of approximately 120 subjects will be enrolled in 1 of 9 cohorts to receive SEL 18 mg once daily (Cohort 1), GS-0976 20 mg once daily (Cohort 2), GS-9674 30 mg once daily with food (Cohort 3), SEL 18 mg + GS-9674 30 mg once daily with food (Cohort 4), SEL 18 mg + GS-0976 20 mg once daily (Cohort 5), GS-9674 30 mg + GS-0976 20 mg once daily with food (Cohort 6), GS-0976 20 mg once daily (Cohort 7), GS-9674 30 mg once daily with food (Cohort 8), or SEL 18 mg + GS-0976 20 mg + GS-9674 30 mg once daily with food (Cohort 9) for 12 weeks.

The primary endpoint is the safety of the study drug(s). CCI [redacted]

Preliminary safety data cohorts evaluating treatments with SEL (Cohorts 1, 4, 5, and 9) from an interim analysis as of 31 January 2018 are presented below.

1.2.8.2. Subject Disposition

As of 31 January 2018, a total of 61 subjects have been enrolled in Cohort 1 (10 subjects), Cohort 4 (20 subjects), Cohort 5 (20 subjects), and Cohort 9 (11 subjects). Among these subjects, 1 enrolled subject in Cohort 9 did not receive study drug. All subjects in Cohorts 1, 4, and 5 have completed study drug, and all 10 subjects in Cohort 9 remain on treatment.

1.2.8.3. Preliminary Safety Results

Adverse events were reported for 5 subjects (50.0%) in Cohort 1, 5 subjects (25.0%) in Cohort 4, 8 subjects (40.0%) in Cohort 5, and 4 subjects (40.0%) in Cohort 9. No deaths or AEs leading to premature discontinuation of study drug were reported.

The 3 most commonly reported AEs across Cohorts 1, 4, 5, and 9 were headache, diarrhea, and constipation. Treatment-related AEs were reported for 3 subjects (30.0%) in Cohort 1, 2 subjects (10.0%) in Cohort 4, 5 subjects (25.0%) in Cohort 5, and 3 subjects (30.0%) in Cohort 9. Treatment-related AEs reported for > 1 subject in Cohorts 1, 4, 5, or 9 included diarrhea (2 subjects [10.0%] in Cohort 5) and headache (2 subjects [20.0%] in Cohort 9).

Serious adverse events were cellulitis in 1 subject in Cohort 4 and tooth abscess in 1 subject in Cohort 5. Neither of these events was considered treatment related.

1.2.9. Adverse Events Pooled Across Nonalcoholic Steatohepatitis Studies GS-US-384-1497 and GS-US-384-3914

In a pooled analysis of AEs across the 2 NASH Studies GS-US-384-1497 and GS-US-384-3914, 72 of 122 (59.0%) subjects who received SEL reported AEs: 46 (50.0%) of those who received SEL 18 mg and 26 (86.7%) of those who received SEL 6 mg. The most common AEs in the pooled SEL group were headache (18 [14.8%] subjects), nausea (12 [9.8%] subjects), constipation, fatigue, and sinusitis (each with 8 [6.6%] subjects).

1.2.10. Study GS-US-384-1943: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of SEL in Subjects with Nonalcoholic Steatohepatitis and Bridging (F3) Fibrosis

Preliminary safety data from an interim analysis of this Phase 3 study in subjects with bridging fibrosis due to NASH as of 12 January 2018 are presented below.

1.2.10.1. Subject Disposition

As of 12 January 2018, a total of 458 subjects have been randomized and 425 subjects have been treated in the randomized phase of the study for a median (min, max) of 11.9 (0.1, 44.1) weeks. Three subjects prematurely discontinued study drug: 2 subjects due to subject decision and 1 subject due to AE. A total of 421 subjects remain on treatment. Because the study is ongoing and blinded, the treatment received by these subjects is unknown.

1.2.10.2. Preliminary Safety Results

This ongoing study is blinded and subject treatment assignment is unknown; therefore, data presented below are pooled across treatment groups.

A total of 217 subjects (51.1%) had at least 1 AE. The majority of AEs were Grade 1 in severity. The most commonly reported AEs were diarrhea (30 subjects, 7.1%), fatigue (24 subjects, 5.6%), and headache (23 subjects, 5.4%). Treatment-related AEs were reported for a total of 85 subjects (20.0%).

One subject experienced an AE (Grade 2 myalgia) leading to discontinuation of study drug. No deaths were reported.

Serious adverse events were reported for 11 subjects (2.6%). No SAE was reported in more than 1 subject, and none of the events were considered treatment related by the investigator.

1.2.11. Study GS-US-384-1944: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of SEL in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis

1.2.11.1. Study Design

Study GS-US-384-1944 is an ongoing Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of SEL in subjects with compensated cirrhosis (F4 fibrosis) due to NASH (defined as the presence of at least grade 1 steatosis, hepatocellular ballooning, and lobular inflammation according to the NAS).

A total of approximately 800 subjects will be randomized in a 2:2:1 ratio into 1 of 3 treatment groups: SEL 6 or 18 mg, or matching placebo administered once daily for 240 weeks.

The primary efficacy endpoint at Week 48 is the proportion of subjects 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). The clinical efficacy endpoint at Week 240 is EFS, which will be assessed by the time to the first clinical event including liver decompensation events, liver transplantation, or all-cause mortality.

Subjects who experience a hepatic clinical event (except all-cause mortality and liver transplantation) prior to completing the Week 240 visit of the randomized phase will be offered the option to rollover into an open-label phase of the study. Each of these clinical events will require confirmation by a Hepatic Events Adjudication Committee.

Preliminary safety data from an interim analysis as of 12 January 2018 are presented below.

1.2.11.2. Subject Disposition

As of 12 January 2018, a total of 696 subjects have been randomized and 656 subjects have been treated in the randomized phase of the study for a median (min, max) of 12.1 (0.1, 51.9) weeks. Four subjects prematurely discontinued study drug: 2 subjects due to investigator's discretion and 2 subjects due to subject decision. A total of 646 subjects remain on treatment in the randomized phase. Six subjects experienced protocol-specified clinical events during the randomized phase and entered the open-label phase of the study; these 6 subjects remain on treatment in the open-label phase.

1.2.11.3. Preliminary Safety Results

This ongoing study is blinded and subject treatment assignment is unknown; therefore, data presented below are pooled across treatment groups.

A total of 357 subjects (54.4%) had at least 1 AE. The majority of AEs were Grade 1 in severity. The most commonly reported AEs were nausea (57 subjects, 8.7%), headache (49 subjects, 7.5%), and diarrhea (40 subjects, 6.1%). Treatment-related AEs were reported for a total of 126 subjects (19.2%).

Adverse events leading to discontinuation of study drug in the randomized phase were reported for 7 subjects (1.1%), 6 of whom met criteria for protocol-specified clinical events and entered the open-label phase of the study.

Serious adverse events were reported for 24 subjects (3.7%). The most common type of SAEs was gastrointestinal disorders (6 subjects, 0.9%). Serious adverse events that were reported in > 1 subject included sepsis (3 subjects, 0.5%) and chest pain and hepatic encephalopathy (each 2 subjects, 0.3%). No SAEs were assessed as treatment related by the investigator. No deaths were reported.

For further information on SEL, refer to the IB for SEL.

1.3. Rationale for This Study

NASH is an increasingly prevalent cause of cirrhosis for which there is no currently approved therapy. The greatest morbidity and mortality due to NASH are observed in patients with advanced fibrosis {Ekstedt 2014, Yeh 2014}. As described by Angulo *et al.*, advanced fibrosis is the only independent prognostic factor associated with mortality and liver-related morbidity in NASH {Angulo 2015}. SEL is a potent and selective small molecule inhibitor of ASK1, a kinase which contributes to oxidative stress-mediated hepatocellular damage, apoptosis, inflammation, and fibrosis in NASH. By inhibiting ASK1 signaling, SEL is expected to cause regression of hepatic fibrosis and delay progression to cirrhosis in subjects with advanced fibrosis. In Phase 2 study GS-US-384-1497, treatment with SEL 18 mg or 6 mg (± SIM 125 mg) led to a ≥ 1-stage decrease in NASH CRN fibrosis stage from baseline in 43% and 30% of subjects, respectively, compared with 20% of subjects treated with SIM alone. Progression to cirrhosis was also less frequent with both SEL doses (3% and 7% for 18 mg and 6 mg, respectively) compared with SIM alone (20%).

To confirm the anti-fibrotic activity of SEL, this Phase 3 study has been designed as a multicenter, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of SEL for 240 weeks in subjects with NASH and advanced fibrosis. Eight hundred subjects with histologically-confirmed NASH and bridging (F3) fibrosis (according to the NASH CRN classification) will be randomized in a 2:2:1 ratio to receive SEL at a dose of 6 mg or 18 mg orally once daily or placebo. Randomization will be stratified by the presence of diabetes mellitus, a common comorbidity in this condition, and ELF™ score (< 9.76 vs. ≥ 9.76) during Screening. In the Phase 2b study GS-US-321-0105 of SIM, an ELF™ score ≥ 9.76 was associated with an increased risk of liver-related clinical events (area under the receiver operating characteristic [AUROC] curve, 0.794). The primary objective of this study is to evaluate whether SEL can cause fibrosis regression and prevent progression to cirrhosis in this high-risk patient population. Efficacy will be determined by changes in liver histology and adjudicated hepatic clinical event rates that include hepatic decompensation, liver transplantation, and all-cause mortality. Due to the increased risk of cardiovascular morbidity and mortality in NASH {Angulo 2015, Ekstedt 2015, Targher 2016}, the impact of SEL on metabolic parameters (e.g., lipids and insulin resistance) will be monitored and cardiovascular events will be prospectively recorded and adjudicated.

1.4. Rationale for Dose Selection of SEL

The doses of SEL chosen for evaluation in this study, 6 mg and 18 mg once daily, are supported by a combination of safety and efficacy data from Phase 1 and 2 studies in the clinical development program, and pharmacokinetic (PK)/pharmacodynamic (PD) modeling of predicted inhibition of p38 phosphorylation, a downstream marker of ASK1 pathway activation. In Phase 2 studies in subjects with PAH and DKD, SEL reduced blood phosphorylated (activated) p38 in a dose-dependent fashion. Based on this exposure-response model, plasma SEL exposures observed in the NASH patients in study GS-US-384-1497 after administration of SEL 6 mg or 18 mg (± SIM 125 mg) would be expected to be associated with 54% and 78% maximal inhibition (E_{max}) of phosphorylated p38, respectively. While the level of inhibition of p38 phosphorylation that is necessary to achieve beneficial effects in NASH is currently unknown, both doses of SEL 6 mg and 18 mg (± SIM 125 mg) administered for 24 weeks in study GS-US-384-1497 demonstrated improved efficacy over SIM alone. For example, the proportion of subjects that achieved a ≥ 1-stage reduction in NASH CRN fibrosis stage was higher than observed in subjects treated with SIM alone (see above). Progression to cirrhosis was also less frequent among SEL-treated subjects. While these data may suggest a dose response, the 6 mg dose had better responses than the 18 mg dose for some endpoints (e.g., ≥15% reduction in liver stiffness by magnetic resonance elastography [MRE]) and the results with prolonged dosing have not yet been established. 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 administered for up to 48 weeks has been well tolerated with no clear dose-safety relationships for incidences or severity of AEs or laboratory abnormalities. However, the complete safety profile of SEL has not been fully characterized given the relatively small number of subjects treated to date. In order to determine a safe and effective dose for patients with advanced fibrosis due to NASH, it is important to establish the correct balance of efficacy and safety in larger studies in this population. For these reasons, testing of both 6 mg and 18 mg SEL once daily in this Phase 3 study is planned to further optimize dose selection for the treatment of NASH-related bridging fibrosis.

1.4.1. Rationale for Study Population

The SEL Phase 3 development program is focused on patients with NASH and advanced fibrosis due to the significant risk of liver-related complications in this patient population. As reported in the PRELHIN study {Angulo 2015}, which examined the natural history of 619 patients with histologically-confirmed NAFLD for a median duration of 12.6 years, the cumulative risk of liver-related events (defined as ascites, varices/variceal bleeding, HE, and HCC) was 14% in patients with F3 fibrosis and 24% in patients with cirrhosis (F4). Event rates in patients with F0, F1, and F2 fibrosis were significantly lower at 1.6%, 2.8%, and 7.1%, respectively. Compared to patients with F0 fibrosis, the adjusted risk of liver-related events was increased over 13-fold in patients with F3 fibrosis and 47-fold in patients with cirrhosis. Similar data have been reported by other groups {Ekstedt 2006, Ekstedt 2015, Hagstrom 2016, Younossi 2011}. At present, no treatment exists for this high risk patient population. Thus, the NASH subjects with the highest unmet need are not currently eligible for any therapy. Targeting interventions to help this population would be expected to have the greatest impact on morbidity and mortality.

1.5. Risk/Benefit Assessment for the Study

This study will provide information regarding the safety and efficacy of SEL for the treatment of patients with bridging fibrosis due to NASH. The potential benefits of SEL for the treatment of NASH were shown in the Phase 2 study GS-US-384-1497. As described above, rapid 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 2015, Ratziu 2016}. In addition, reductions in liver biochemistries (e.g., ALT, aspartate aminotransferase [AST], gamma glutamyl transferase [GGT], liver fat content by magnetic resonance imaging-proton density fat fraction [MRI-PDFF], lobular inflammation, liver stiffness by magnetic resonance elastography [MRE],and biomarkers of apoptosis and necrosis (serum CK-18 M30 and M65 levels) were observed, particularly in fibrosis responders.

Subjects randomized to the placebo control arm in the study may benefit from frequent medical monitoring and close assessment of their NASH and associated pathologies during the duration of placebo treatment. For example, the identification of progression to cirrhosis during this trial will trigger close monitoring for complications of cirrhosis (e.g., esophageal varices and HCC) that may not otherwise be performed. Moreover, all subjects, including those treated with placebo during the Randomized Phase, have the opportunity to receive SEL treatment during the Open-Label Phase in the event of progression to cirrhosis.

Potential risks of this study include those related to the fact that SEL is a new chemical entity with a long term safety profile that has yet to be established. In nonclinical studies, profuse diarrhea was the dose limiting toxicity in cynomolgus monkeys. In Phase 2 clinical studies in AH, PAH, DKD, and NASH, a greater proportion of subjects treated with SEL (66 of 565 [11.7%]) had an adverse event of diarrhea compared to placebo- or SIM-treated subjects (13 of 184 [7.1%]). However, diarrhea was generally mild and self-limited. Across the development program, drug discontinuation rates were low and not attributable to a single AE with increased frequency. In Phase 2 clinical studies in subjects with NASH, AH, DKD, or PAH, rates of elevations in liver tests (ALT or AST > 3 × upper limit of normal [ULN] and > 2 × baseline for the NASH studies; ALT or AST > 5 × baseline for the AH study; ALT or AST > 3 × ULN for the DKD and PAH studies) were observed in SEL-treated subjects (17 of 564 [3.0%]) and placebo-treated subjects (4 of 182 [2.2%]). In many of these cases, an alternative and/or confounding etiology was identified including alcohol use, intercurrent illness, or concomitant treatment with medications known to cause hepatotoxicity. However, in some cases, a plausible alternate etiology was not identified. To mitigate the potential risk of liver injury in the planned Phase 3 NASH program, subjects will be monitored closely; defined rules for close observation and drug cessation due to elevated liver tests have been specified in Section 7.5; and all potential cases of drug-induced liver injury (DILI) will be adjudicated by an independent DILI adjudication committee. In addition, embryofetal toxicity was observed in nonclinical studies; therefore to prevent potential fetal exposure, adherence to effective methods of contraception will be required during the Phase 3 program.

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.

While the potential benefits and risks described above must be confirmed during the Phase 3 program, available data in NASH patients treated for 24 weeks, as well as the favorable safety profile seen across the Phase 2 studies in NASH, DKD, and PAH, provide strong rationale for a positive benefit/risk ratio in support of the study in subjects with bridging fibrosis due to NASH.

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate whether SEL can cause fibrosis regression and reduce progression to cirrhosis and associated complications in subjects with NASH and bridging (F3) fibrosis.

The secondary objective of this study is:

- To assess the safety and tolerability of SEL in subjects with NASH and bridging (F3) fibrosis.

The exploratory objectives of this study are as follows:


CCI

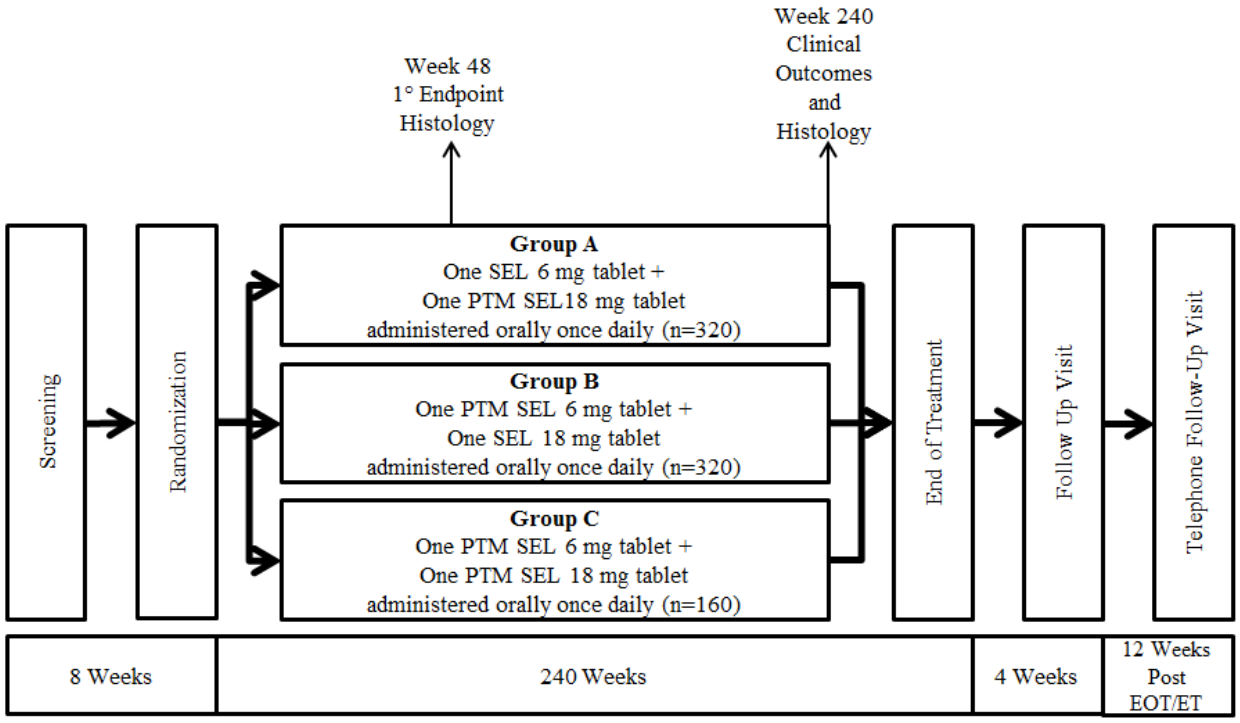
3. STUDY DESIGN

3.1. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of SEL in subjects with NASH and bridging (F3) fibrosis.

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

Figure 3-1. Overall Study Design



3.2. Treatment Plan and Regimen

Subjects meeting the study's entry criteria will be randomly assigned in a 2:2:1 ratio to 1 of 3 treatment groups: Group A, Group B and Group C 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 Screening lab values if previously undiagnosed [i.e. hemoglobin A1c (HbA1c) ≥ 6.5% or fasting plasma glucose ≥ 126 milligram/deciliter [mg/dL]) and by ELF™ score ≥ 9.76 or < 9.76 during Screening. Study drugs will be administered for up to a total of 240 weeks.

3.3. Adjudication Committees

3.3.1. Hepatic Events Adjudication Committee

A key primary objective of this study is to prevent progression to cirrhosis and associated complications. A composite of clinical events that constitute the clinical efficacy endpoint have been identified and include:

1) Progression to cirrhosis as defined by a liver biopsy showing F4 fibrosis according to the NASH CRN classification, as assessed by the central reader.

2) Events of hepatic decompensation including:

   a) Clinically apparent ascites requiring treatment

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

   c) 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

3) Liver transplantation or qualification for liver transplantation, defined as MELD score ≥ 15 on at least 2 consecutive occasions at least 4 weeks apart

4) All-cause mortality

Each of the clinical events (except histologic progression to cirrhosis, all-cause mortality and liver transplantation) will require confirmation by a Hepatic Events Adjudication Committee. All deaths will be reviewed by this committee to determine if they are liver-related. Subjects who experience one of these confirmed clinical events prior to completing the Week 240 Visit of the Randomized Phase will be offered the option to rollover into an Open-Label (OL) Phase of the study. The committee will also review all cases of HCC in the Randomized Phase as an event of special interest.

If there is clinical evidence that a subject has progressed to cirrhosis (e.g., based on the presence of new esophageal varices, changes in biomarkers [including, but not limited to, low serum albumin, high serum bilirubin, a low platelet count, prolonged INR, or elevated liver stiffness], or development of other clinical signs or symptoms of cirrhosis), the subject should undergo repeat liver biopsy for confirmation of progression to cirrhosis (F4 fibrosis as assessed by the central reader according to the NASH CRN classification) at the discretion of the primary investigator (PI).

Once the clinical event (except histological progression to cirrhosis, all-cause mortality and liver transplantation) is confirmed by the Hepatic Events Adjudication Committee, the subject will no longer participate in the Randomized Phase and will be offered the option to receive SEL 18 mg in the OL Phase for a total treatment duration of 240 weeks inclusive of the Randomized Phase.

Rollover into the OL Phase of the study must occur within 60 days of confirmation of the event. Subjects starting the OL Phase of the study will complete the same study procedures as during the Randomized Phase of the study, starting with the Day 1 visit with the exception of the liver biopsy CCI [redacted] Hepatic clinical events will be adjudicated and deaths will be reviewed by the Hepatic Events/DILI Adjudication Committee only during the Randomized Phase of the study; potential DILI events and cardiovascular events including deaths will continue to be adjudicated in the OL Phase by the Hepatic Events/DILI Adjudication Committee and the Cardiovascular Events Adjudication Committee, respectively.

3.3.2. Cardiovascular Events Adjudication Committee

Cardiovascular events including cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for cardiac failure, and coronary revascularization will be adjudicated by an independent Cardiovascular Events Adjudication Committee. Subjects experiencing a cardiovascular event will continue in the Randomized Phase and not rollover into the OL Phase. Cardiovascular events will be adjudicated during the Randomized Phase and the OL Phase of the study.

3.3.3. Drug-Induced Liver Injury (DILI) Adjudication Committee

Due to the challenge of recognizing and diagnosing DILI in subjects with pre-existing hepatic dysfunction, a DILI Adjudication Committee will review potential cases of DILI (refer to Section 7.5). Subjects will be categorized as those for whom DILI or worsening of hepatic function attributable to study drug could be excluded (e.g., a clear, alternative explanation exists); those for whom DILI or worsening of hepatic function attributable to study drug could not be excluded (e.g., no clear, alternative explanation exists); and those with insufficient data to make a determination. Potential cases of DILI will be adjudicated during the Randomized Phase and the OL Phase of the study.

3.4. Biomarker Testing

3.4.1. Biomarker Samples to Address the Study Objectives

CCI [redacted]

Table 3-1. Exploratory Biomarkers

[redacted]

3.4.2. Biomarker Samples for Optional Future Research

[redacted]

3.4.3. Biomarker Samples for Optional Genomic Research

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[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will enroll approximately 800 subjects with NASH and bridging (F3) fibrosis.

4.2. Inclusion Criteria

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

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

2) Liver biopsy consistent with NASH (defined as the presence of at least grade 1 steatosis, hepatocellular ballooning, and lobular inflammation according to the NAFLD Activity Score [NAS]) and bridging (F3 fibrosis) according to the NASH CRN classification, in the opinion of the central reader

    a) A historical liver biopsy within 6 months of the Screening visit may be accepted as the Screening biopsy if the sample is deemed acceptable for interpretation by the central reader

    b) If the subject is deemed ineligible for this study, the liver biopsy, if performed according to protocol specifications and is within 12 months of the Screening visit, may be used to determine eligibility for study GS-US-384-1944

3) Subject has the following laboratory parameters at the Screening visit, as determined by the central laboratory:

    a) ALT ≤ 8 x ULN

    b) CL_{cr} ≥ 30 mL/min, as calculated by the Cockcroft-Gault equation

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

    d) Total bilirubin ≤ 1.3 x ULN (unless an alternate etiology such as Gilbert's syndrome or hemolytic anemia is present)

    e) INR ≤ 1.4, unless due to therapeutic anti-coagulation

    f) Platelet count ≥ 100,000/µL

4) Body Mass Index (BMI) ≥ 18 kg/m^2 at Screening

5) Males and non-pregnant, non-lactating females between 18-70 years of age; inclusive based on the date of the Screening visit

6) Females of childbearing potential (as defined 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) Prior history of decompensated liver disease, including clinical ascites, HE, or variceal bleeding

2) CP score > 6, as determined at Screening, unless due to therapeutic anti-coagulation

3) MELD score > 12, as determined at Screening, unless due to therapeutic anti-coagulation

4) Chronic HBV infection (HBsAg positive)

5) Chronic HCV infection (HCV Ab and HCV RNA positive). Subjects cured of HCV infection less than 5 years prior to the Screening visit are not eligible

6) Other causes of liver disease including, but not limited to, alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders (e.g., primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis), drug-induced hepatotoxicity, Wilson disease, iron overload, and alpha-1-antitryspin deficiency, based on medical history and/or centralized review of liver histology

7) History of liver transplantation

8) Current or history of HCC

9) Any weight reduction surgery in the 2 years prior to Screening or planned during the study (weight reduction surgery is disallowed during the study), and malabsorptive weight loss surgery (e.g., Roux-en-Y or distal gastric bypass) at any time prior to Screening

10) Weight loss > 10% within 6 months of Screening

11) HIV infection (HIV Ab and HIV ribonucleic acid [HIV RNA] positive)

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

13) Positive urine drug screen for amphetamines, cocaine or opiates (i.e. 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 opioid-based medication are eligible if the prescription and diagnosis are reviewed and approved by the investigator

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

    a) Unstable angina, myocardial infarction, coronary artery bypass graft surgery or coronary angioplasty within 6 months prior to 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.

15) Use of any prohibited concomitant medication as described in Section 5.4. Subjects on Vitamin E must be on a stable dose 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 diagnostic liver biopsy

16) 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

17) Unable to safely undergo a liver biopsy

18) Participation in another investigational study of a drug or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Screening

19) Concurrent participation in another therapeutic clinical study

20) Known hypersensitivity to SEL, the metabolites, or formulation excipient

21) Any laboratory abnormality or condition that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results

22) Presence of any 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 or a psychiatric condition requiring hospitalization 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

This is a randomized, double-blind, placebo-controlled study. Subjects meeting the study's entry criteria will be randomly assigned in a 2:2:1 ratio to 1 of 3 treatment groups as described in Section 5.3.

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web Response System (IWRS) will be used for centralized randomization and treatment assignment. Randomization will be stratified by the presence or absence of diabetes mellitus (as determined by medical history or based on Screening lab values if previously undiagnosed [i.e., HbA1c ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dL]) and by ELF™ score ≥ 9.76 or < 9.76 during Screening.

ELF™ score will not be provided to the sites. Stratification will be performed by the IWRS.

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

Study drugs during the Randomized Phase will be dispensed by the study pharmacist, or designee, 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 IWRS system for that subject (refer to Study Reference Binder for IWRS unblinding instructions). 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 and on the electronic case report form (eCRF), 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.

Gilead Pharmacovigilance and Epidemiology (PVE) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Selonsertib (SEL)

5.2.1. Formulation

5.2.1.1. Selonsertib (SEL) 6 mg

SEL 6 mg tablets will be supplied as pentagon-shaped, film-coated gray tablets debossed with an underscored "6" on one side and "GSI" on the other side. The tablets have dimensions of approximately 6.4 mm x 6.4 mm. In addition to the active ingredient, SEL 6 mg tablets contain the following inactive ingredients: PPD

PTM SEL 6 mg tablets are available for blinding purposes. Each placebo tablet is identical to SEL 6 mg tablets in their size, shape, and appearance and contains the same inactive ingredients.

5.2.1.2. Selonsertib (SEL) 18 mg

SEL 18 mg tablets will be supplied as round, film-coated gray tablets debossed with an underscored "18" on one side and "GSI" on the other side. The tablets are approximately 7.14 mm in diameter. In addition to the active ingredient, SEL 18 mg tablets contain the following inactive ingredients: PPD

PTM SEL 18 mg tablets are available for blinding purposes. Each placebo tablet is identical to SEL 18 mg tablets in their size, shape, and appearance and contains the same inactive ingredients.

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.

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), European Union (EU) Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

SEL and PTM SEL 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.

5.3. Dosage and Administration of Selonsertib (SEL)/ PTM Selonsertib (SEL)

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

5.3.1. Selonsertib (SEL)/PTM Selonsertib (SEL)

SEL and PTM SEL tablets will be provided by Gilead Sciences. Subjects will take one tablet each of SEL (18 mg or PTM 18 mg and 6 mg or PTM 6 mg) once daily at approximately the same time each day. Study drug should be swallowed whole with water and may be taken with or without food. A dose will be considered missed if the subject cannot take the 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 6 mg tablet + one PTM SEL 18 mg tablet administered orally once daily
- Treatment Group B: one PTM SEL 6 mg tablet + one SEL 18 mg tablet administered orally once daily
- Treatment Group C: one PTM SEL 6 mg tablet + one PTM SEL 18 mg tablet administered orally once daily

5.4. 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 to the end of the follow-up period.

The following medications are prohibited for all treatment groups:

- Any investigational medication or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Screening and throughout the study. 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/S001), once approved by the applicable IRB/IEC.
- Strong cytochrome P4503A4 (CYP3A4) inducers may decrease the exposure of SEL and could lead to decreased efficacy. Use of strong CYP3A4 inducers is prohibited from 2 weeks prior to Day 1 through end of treatment.

Caution should be exercised when co-administering sensitive P-gp substrates with narrow therapeutic index with SEL 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 must be on a stable dose for at least 6 months prior to the diagnostic liver biopsy and 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.

Examples of representative medications that are prohibited from 2 weeks prior to Day 1 as well as specific medications which are prohibited or which should be used with caution from 30 days prior to Day 1 are listed below in Table 5-1**.**

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

Agents Disallowed	
Drug Class	**Medications Disallowed 2 weeks prior to Day 1 through the end of treatment**
Anticonvulsants[b]	phenobarbital, phenytoin, carbamazepine
Antimycobacterials[b]	rifampin, rifabutin, rifapentine[c]
Herbal/Natural Supplements[b]	St. John's Wort, Echinacea
Drug Class	**Medications Disallowed 30 days prior to Day 1 through the end of treatment**
Select chronic immunosuppressants	Chronic systemic[d]- corticosteroids, tacrolimus, sirolimus, cyclosporine, mycophenolate mofetil, and methotrexate
Farnesoid X receptor (FXR) agonists, Peroxisome Proliferator-Activated Receptor (PPAR) agonists, Chemokine Receptor (CCR) 2/5 inhibitors	obeticholic acid[c], elafibranor[c], and cenicriviroc[c]
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], ranolazine[c], dabigatran etexilate, aliskiren

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 May result in a decrease in the concentration of SEL
c Not approved in Japan
d Intra-articular, topical, nasal, epidural or inhaled routes are allowed. Chronic systemic use of corticosteroids equivalent to prednisone > 10mg/day for > 2 weeks is not allowed.
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.

5.5. Accountability for Selonsertib (SEL)/PTM Selonsertib (SEL)

The investigator or designee (e.g., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug bottles. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Gilead Sciences and quantities dispensed to subjects, including the lot/kit number, date dispensed, subject identification number, subject initials, and the initials of the person dispensing the medication. All used and unused study drug bottles dispensed to subjects must be returned to the site.

5.5.1. 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 drug 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 enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

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

6.1. Subject Enrollment and Treatment Assignment

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

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

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

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 8 weeks prior to 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 labs may be repeated once within the Screening period, at the discretion of the investigator, prior to administration of study drugs.

Screening information from Study GS-US-384-1944 of SEL in NASH may be used to determine eligibility and fulfill Screening visit assessments for this study if obtained within the Screening window.

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 before initiation of any Screening procedures
- Review and record whether the subject meets inclusion and exclusion criteria

- Obtain Screening number from IWRS
- Obtain medical history
- Complete PE
- Record vital signs, waist circumference, body weight, and height
- Conduct standard 12-Lead ECG
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - HIV-1, HBV and HCV serology
  - HbA1c
  - eGFR
  - Biomarkers
  - Serum pregnancy test (only for female subjects of childbearing potential; see Appendix 3)
- Collect urine samples for:
  - Urine drug screen for amphetamines, cocaine and opiates (i.e., heroin, morphine)
- Assess ascites and HE
- CP and MELD scores
- Perform liver biopsy and provide liver tissue for central reading (if required). A historical biopsy within 6 months of the Screening visit may be accepted as the Screening biopsy if the sample is deemed acceptable for interpretation and consistent with NASH-related bridging fibrosis by the central reader
- Record all concomitant medications that the subject has taken within 30 days prior to Screening
- CCI [redacted]

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events eCRF.

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

6.3. Baseline Assessments

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 Day 1 visit to ensure an approximate 8-hour fast prior to the blood sample collection the next morning.

After review of inclusion and exclusion criteria to confirm continued eligibility, subjects will be randomized to study drug assignment and receive their Subject Identification Number via the IWRS prior to their first dose of study drugs.

Randomization will be stratified by the presence or absence of diabetes mellitus (as determined by medical history or based on Screening lab values if previously undiagnosed [i.e., HbA1c ≥ 6.5% OR fasting plasma glucose ≥ 126 mg/dL]) and by ELF™ score ≥ 9.76 or < 9.76 during Screening.

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

- HRQoL Questionnaires (SF-36, WPAI, CLDQ-NAFLD, and EQ-5D)
  - Note: It is recommended that HRQoL Questionnaires be completed prior to any study procedures being performed and prior to the subject seeing a health care provider.
- Health Resource Utilization Questionnaire
- Symptom driven PE
- Record vital signs, waist circumference, and body weight
- Record subject's stool frequency
- Provide lifestyle modification counseling
- Obtain blood saelastmples for:
  - Chemistry
  - Hematology

  - Coagulation Panel
  - Insulin and Lipids
  - HbA1c
  - eGFR
  - Single PK sampling:
    - OL Phase, in subjects with severe hepatic impairment (Child-Pugh Class C) in combination with renal impairment (eGFR < 30 mL/min)
  - Biomarkers

- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Biomarkers, albumin, creatinine and albumin/creatinine ratio
- CCI [redacted]
- Assess ascites and HE
- MELD score
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring since the Screening visit
- Dispense study drugs to the subject and provide instruction on appropriate dosing and administration; subject will take the Day 1 dose of study drugs on-site
- CCI [redacted]
- Abdominal ultrasound imaging (OL phase only, to be done after subject has confirmed they will rollover and prior to or on Day 1)

6.4. Treatment Assessments

6.4.1. Week 1 Visit

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:

- Symptom driven PE
- Record vital signs, and body weight
- Record subject's stool frequency
- Provide lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - eGFR
  - Single PK sampling:
    - Randomized Phase at Week 1 in all subjects
    - OL Phase, in subjects with severe hepatic impairment (Child-Pugh Class C) in combination with renal impairment (eGFR < 30 mL/min)
- Assess ascites and HE
- MELD score
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events occurring since the previous visit
- Review of study drug dosing compliance (pill count)

6.4.2. Week 4, Week 12, Week 24, Week 72, Week 120, Week 168 and Week 216 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.

The following will be performed and documented at this visit:

- HRQoL Questionnaires (SF-36, WPAI, CLDQ-NAFLD, and EQ-5D, not performed at Week 4)
- Health Resource Utilization Questionnaire (not performed at Week 4)
- Symptom driven PE
- Record vital signs, waist circumference, and body weight
- Record subject's stool frequency
- Provide lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Insulin and Lipids
  - HbA1c
  - eGFR
  - Biomarkers (Weeks 12 and 24)
  - Single PK sampling:
    - Randomized Phase at Weeks 4, 12, and 24 in all subjects
    - OL Phase, at all visits in subjects with severe hepatic impairment (Child-Pugh Class C) in combination with renal impairment (eGFR < 30 mL/min)
  - CCI [redacted]

- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Biomarkers, albumin, creatinine and albumin/creatinine ratio (Week 12 and Week 24 only)
- Assess ascites and HE
- MELD score
- Abdominal ultrasound (OL Phase only at Week 24, Week 72, Week 120, Week 168 and Week 216)
- Perform liver stiffness measurement by elastography (if available, Week 24 only)
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events 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

6.4.3. Week 8, Week 36, Week 44, Week 60, Week 84, Week 108, Week 132, Week 156, Week 180, Week 204 and Week 228 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.

The following will be performed and documented at this visit:

- Symptom driven PE
- Record vital signs, and body weight
- Record subject's stool frequency
- Provide lifestyle modification counseling

- Obtain blood samples for:
  - — Chemistry
  - — Hematology
  - — Coagulation Panel
  - — eGFR
  - — Single PK sampling:
    - OL Phase, at all visits in subjects with severe hepatic impairment (Child-Pugh Class C) in combination with renal impairment (eGFR < 30 mL/min)
- Collect urine sample for:
  - — Urine pregnancy test for females of childbearing potential only
- Assess ascites and HE
- MELD score
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events 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

6.4.4. Week 16, Week 20, Week 28, Week 32 and Week 40 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.

The following will be performed and documented at this visit:

- Symptom driven PE
- Record vital signs, and body weight
- Record subject's stool frequency
- Provide lifestyle modification counseling

- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - eGFR
  - Single PK sampling:
    - OL Phase, at all visits in subjects with severe hepatic impairment (Child-Pugh Class C) in combination with renal impairment (eGFR < 30 mL/min)
- Collect urine sample for:
  - Urine pregnancy test for females of childbearing potential only
- Assess ascites and HE
- MELD score
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events 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

6.4.5. Week 48, Week 96, Week 144, Week 192 and Week 240 (End of Treatment [EOT]) Visits

Subjects in the Randomized or OL phase who are completing 240 weeks on study should complete the Week 240/EOT visit assessments.

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:

- HRQoL Questionnaires (SF-36, WPAI, CLDQ-NAFLD, and EQ-5D)
- Health Resource Utilization Questionnaire

- Symptom driven PE
- Record vital signs, waist circumference, and body weight
- Record subject's stool frequency
- Provide lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Insulin and Lipids
  - HbA1c
  - eGFR
  - Biomarkers
  - Single PK sampling:
    - Randomized Phase at Week 48 in all subjects
    - OL Phase, at all visits in subjects with severe hepatic impairment (Child-Pugh Class C) in combination with renal impairment (eGFR < 30 mL/min)
- CCI [redacted]
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Biomarkers, albumin, creatinine and albumin/creatinine ratio
- Assess ascites and HE
- MELD score
- Perform liver biopsy and provide liver tissue for central reading (Randomized Phase at Week 48 and Week 240 Visits only)
- Perform liver stiffness measurement by elastography (if available)

- Abdominal ultrasound (OL phase only)
- Dispense study drugs to the subject and provide instruction on appropriate dosing and administration (not performed at Week 240/EOT)
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events occurring since the previous visit
- Review of study drug dosing compliance (pill count)

6.4.6. Early Termination (ET) Visit

Subjects prematurely discontinuing from the study should complete an ET visit within 30 days of last dose.

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:

- HRQoL Questionnaires (SF-36, WPAI, CLDQ-NAFLD, and EQ-5D)
- Health Resource Utilization Questionnaire
- Symptom driven PE
- Record vital signs, waist circumference, and body weight
- Record subject's stool frequency
- Provide lifestyle modification counseling
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Insulin and Lipids
  - HbA1c
  - eGFR

  - Biomarkers
  - Single PK sampling (all subjects in Randomized Phase and subjects in OL Phase who have severe hepatic impairment [Child-Pugh Class C] and renal impairment [eGFR < 30 mL/min])
- CCI [redacted]
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Biomarkers, albumin, creatinine and albumin/creatinine ratio
- Assess ascites and HE
- MELD score
- At the discretion of the investigator, perform liver biopsy and provide liver tissue for central reading
- At the discretion of the investigator, abdominal ultrasound (OL phase only)
- Perform liver stiffness measurement by elastography (if available)
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events occurring since the previous visit
- Review of study drug dosing compliance (pill count)

6.4.7. 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

Subjects will return for a Follow-Up visit, four weeks after the Week 240/EOT or ET visit.

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
- Record vital signs, and body weight
- Record subject's stool frequency
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - eGFR
- Collect urine sample for:
  - Urine pregnancy test for female subjects of childbearing potential only
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse occurring since the previous visit

6.5.2. Telephone Follow-Up Visit

A Telephone Follow-Up visit will be performed 12 weeks after the Week 240/EOT or ET visit.

The following will be performed and documented at this visit:

- Record any serious adverse events and all adverse events occurring since the previous visit

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

6.6. Visit Windows

The study visit windows are listed below in Table 6-1.

Table 6-1. Visit Windows

Study Visit	Window
Screening Visit	≤ 8 weeks prior to Day 1, window begins with the signing of the informed consent.
Day 1	Day of randomization and first dose of study drugs. All on-treatment study visits are calculated based on the Day 1 date.
Week 48 and Week 240/EOT	(-) 14 days
ET Visit	Within 30 days of last dose of study drug.
All study visits prior to Week 48	± 3 days
All other study visits	± 7 days

6.7. Open-Label Phase

Subjects who progress to cirrhosis on liver biopsy or experience a hepatic clinical event (refer to Section 3.2) prior to completing the Week 240 Visit of the Randomized Phase will be offered the option to rollover into an Open-Label (OL) Phase of the study. Each of the clinical events (except death and liver transplantation) will require confirmation by a Hepatic Events Adjudication Committee. All deaths will be reviewed by this committee to determine if they are liver-related.

Subjects who undergo liver transplantation are not eligible to participate in the OL Phase of the study and should discontinue from the study immediately. Subjects who have permanently discontinued study drugs are not eligible for the OL Phase of the study.

Once a clinical event (except histological progression to cirrhosis, death and liver transplantation) is confirmed by the Hepatic Events Adjudication Committee, the subject will no longer participate in the Randomized Phase and will be offered the option to receive SEL 18 mg in the OL Phase for a total treatment duration of 240 weeks inclusive of the Randomized Phase.

Rollover into the OL Phase of the study must occur within 60 days of confirmation of the event. Subjects starting the OL Phase of the study will complete the same study procedures as during the Randomized Phase of the study, CCI [redacted]. Hepatic clinical events will be adjudicated and deaths will be reviewed by the Hepatic Events/DILI Adjudication Committee only during the Randomized Phase of the study; potential DILI events and cardiovascular events including deaths will continue to be adjudicated in the OL Phase by the Hepatic Events/DILI Adjudication Committee and the Cardiovascular Events Adjudication Committee, respectively.

6.8. Criteria for Discontinuation of Study Treatment

Study medication must be discontinued in the following instances:

- Subject who develops a serious adverse event 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
- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject or investigator request to discontinue for any reason
- Significant subject noncompliance
- Significant protocol violation that impacts subject safety
- Pregnancy during the study; refer to Appendix 3
- Discontinuation of the study at the request of Gilead, a regulatory agency or IRB/IEC/EC

Subjects who discontinue study treatment should be encouraged to complete study visits through Week 240, Follow-Up and a Telephone Follow-Up.

6.9. Assessments for Premature Discontinuation from Study

Subjects prematurely discontinuing from the study should complete an ET visit within 30 days of last dose, a Follow-Up visit 4 weeks later, and a Telephone Follow-Up visit 12 weeks after the ET visit.

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

6.10. Optional Intensive PK Substudy

CCI [redacted]

6.11. Description of Assessments

6.11.1. Clinical Laboratory Analytes

Fasting is required prior to all study visits.

Chemistry:

ALT, AST, albumin, ALP, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid and GGT.

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, prothrombin time (PT), and activated partial thromboplastin time (APTT).

Additional Tests:

HIV-1 (reflex to HIV-1 RNA), HBV (HBsAg), HCV (reflex to HCV RNA) serology, urine drug screen (for amphetamines, cocaine, methadone, opiates), homeostasis model assessment of insulin resistance (HOMA-IR, based on fasting glucose and insulin), eGFR as calculated by Cockcroft-Gault, C-peptide, lipid panel, insulin, free fatty acids, digoxin (for those taking digoxin), creatine phosphokinase, and HbA1c (or serum fructosamine if HbA1c is unable to be resulted).

Biomarker Tests:

Including but are not limited to C-reactive protein (CRP), ELF™, and FibroSURE/FibroTest®.

Urine samples:

Will be collected for albumin, creatinine, albumin/creatinine ratio and stored for future biomarker testing.

Pharmacokinetic (PK) Assessments:

Single PK samples will be collected for PK analysis of SEL and other metabolites, as applicable.

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, 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.

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

6.11.3. Vital Signs

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

Blood pressure will be measured using the following standardized process:

- 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.

6.11.4. Medical History

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

6.11.5. Clinical Liver Assessments

The MELD and CP scores will be calculated from the central laboratory values attained at each visit. CP will be calculated by the site at Screening to assess eligibility; MELD may also be calculated by the sites at Screening to determine eligibility if the central laboratory is unable to perform the calculation. During the OL phase, if the previous eGFR < 30 mL/min, then CP will be calculated by the site (using labs from previous visit and current assessment of HE and ascites); if CP class is C, single PK samples are required for all remaining OL visits through EOT and CP does not need to be calculated at subsequent OL visits. MELD will be monitored by site at each visit for hepatic clinical events requiring adjudication. Assessment of ascites and HE will be determined by the site at all visits, except the Follow-Up and the Telephone Follow-Up visit, as in the Table 6-2 and will be entered into the eCRF. Dialysis in the preceding week will also be determined by the site at each visit. HE will also be assessed using the West Haven Criteria (Appendix 5).

MELD will be calculated using the following formula:

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

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

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

Table 6-2. Child-Pugh Classification of the severity of cirrhosis

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

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

CP class: A = 5-6 points
B = 7-9 points
C = 10-15 points

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

6.11.6. Creatinine Clearance/eGFR

eGFR is estimated by creatinine clearance calculated by 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. Genomic Testing

From subjects who agree to participate and provide consent, blood samples will be collected at the Day 1 visit and at Weeks 48, 96, 144, 192, 240, and ET (if applicable) for genomic testing, including DNA methylation.

6.11.8. Pregnancy Testing

All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 (prior to dosing) and every 4 weeks thereafter. Starting at the Week 48 visit, urine pregnancy testing kits will be provided for home testing every 4 weeks, between in-clinic study visits. All females of childbearing potential will be contacted every 4 weeks and asked to report the result of the urine pregnancy tests. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drug immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

6.11.9. 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. SF-36

The SF-36 asks 36 questions to measure functional health and well-being from the subject's point of view and 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. 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. WPAI

The Work Productivity and Activity Impairment (WPAI) questionnaire asks 6 questions regarding the effect of NASH on a person's ability to work and perform regular activities.

6.11.9.4. 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. Health Resource Utilization Questionnaire

The Healthcare Resource Utilization Questionnaire is designed to assess healthcare usage during the previous three months across a number of direct medical cost domains. This questionnaire should be completed by the patient prior to any procedures being performed at the visit, if possible.

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.

6.11.12. Liver Stiffness Measurement by Elastography

Acceptable elastographic methods include transient elastography (FibroScan®), MRE, acoustic radiation force impulse (ARFI) imaging, and shear-wave elastography (SWE). At each visit, median liver stiffness (in kilopascals (kPa) and/or shear wave velocity (in m/s) will be recorded as applicable. For individual subjects, the same device must be used for all assessments. If FibroScan® is used, liver stiffness should be measured using both the M and XL probes, if available, at the same location on the body. Where available, the median Controlled Attenuation Parameter (CAP) value will be recorded from FibroScan® examinations. Two to three hours of fasting is recommended prior to all elastography assessments.

6.11.13. 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. A historical biopsy within 6 months of the Screening visit 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 will be 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. Histology results from local readers will be collected, if available.

If the liver biopsy is deemed unacceptable by the central reader, it may be repeated.
On-treatment liver biopsy results will be blinded to the investigator and subject unless the subject progresses to cirrhosis (F4 fibrosis). CCI [redacted].

If a liver biopsy is performed per standard of care outside of protocol mandated assessments (e.g., to confirm clinical suspicion of progression to cirrhosis), all possible attempts should be made to submit the biopsy specimen to the central reader for evaluation. If progression to cirrhosis is confirmed by the central reader, the subject will be offered the opportunity to rollover into the OL Phase of the study.

Please refer to the Study Procedures Manual for additional information.

6.11.14. Stool Frequency Assessment

The partial Mayo Score is a survey for the assessment of inflammatory bowel disease (IBD) that contains domains for stool frequency, rectal bleeding, and physician's global assessment. For this study, only the stool frequency subscore will be collected, and "0" should be recorded if a subject has fewer stools than normal. Subject reported scores will be documented in the source documents.

Table 6-3. Stool Frequency Subscore of Partial Mayo Score

Domain	Description	Score
Stool Frequency (based on the past 3 days)	Normal number of stools	0
	1-2 stools more than normal	1
	3-4 stools more than normal	2
	5 or more stools more than normal	3

6.12. Esophagogastroduodenoscopy (EGD)

If an EGD is performed as per standard of care, the data will be recorded in the eCRF. Specific data elements to be recorded include the date of the procedure, and the presence and size of esophagogastric varices.

6.13. Lifestyle Modification Counseling

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

6.14. End of Study Definition

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

6.15. Sample Storage

Residual biological samples from all visits will be frozen and stored if specific consent is obtained. These stored samples may be used by Gilead or research partners of Gilead to help answer questions about the study drugs, NASH, and its associated conditions, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without express consent of the study subjects. At the conclusion of this study, these samples may be retained in storage for Gilead for a period of up to 15 years.

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, 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 (e.g., 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 case report form (CRF)

7.1.2. Serious Adverse Events

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

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it 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

  — 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 (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to investigational medicinal product (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 (e.g., 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 (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

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 describing the event as either unrelated (No) or related (Yes) consistent with the following definitions:

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

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

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

The relationship of an AE or SAE to study procedures (e.g., 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, (e.g., 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). Refer to the Study Reference Binder for additional CTCAE information (see Appendix 4).

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

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

Requirements for collection prior to study drug initiation:

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

Adverse Events

Following initiation of study medication and throughout the duration of the study, including the protocol-required post-treatment follow-up period, all AEs, regardless of cause or relationship, must be collected and reported on the eCRF 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 occurs after the subject first consents to participate in the study (i.e., 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 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 throughout the duration of the study, including the protocol-required post-treatment follow-up period, 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.

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

<u>Electronic Serious Adverse Event (eSAE) Reporting Process</u>

- 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, i.e., the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead Sciences PVE:	Fax:	PPD
	Email:	PPD

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

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

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

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

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, 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 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 IRB/IEC/EC 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 investigator's brochure or relevant local label as applicable.

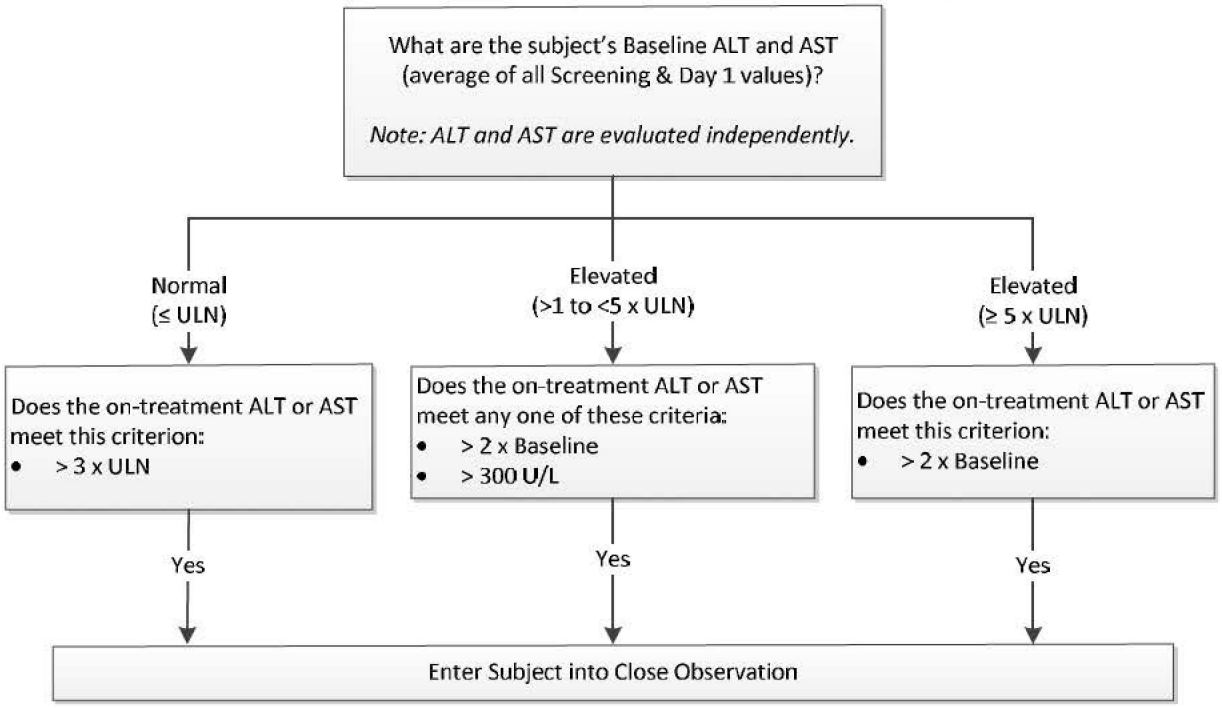
All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB/IEC/EC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional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

7.5. Toxicity Management

At baseline, some subjects may have liver biochemistry levels above the upper limit of normal (ULN). Baseline values for liver tests (ALT, AST, and total bilirubin) will be determined by averaging the values obtained at Screening and Day 1.

If no other cause of the laboratory abnormalities is immediately apparent, on-treatment elevations of ALT and/or AST should be confirmed with repeat testing within 48-72 hours. Subjects with ALT or AST elevations as per Figure 7-1 must be placed into close observation (as described below).

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



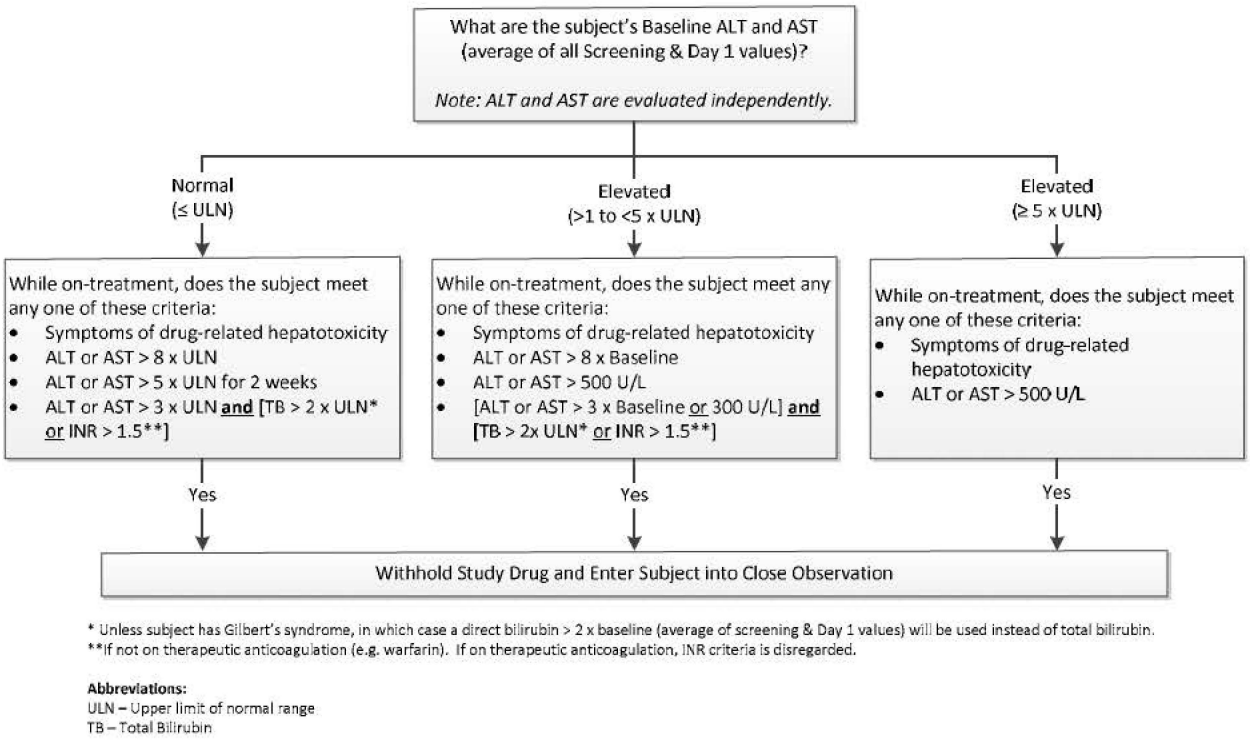
Close observation includes:

- Repeating liver biochemistries (ALT, AST, ALP, GGT, total bilirubin, INR) and obtaining a creatine phosphokinase (CPK) level within 48-72 hours of results
- Obtaining a more detailed history of symptoms and prior or concurrent disease
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtaining a history of exposure to environmental chemical agents
- Ruling out other causes of liver disease as needed (obtain viral hepatitis panel, imaging for evaluation of biliary tract disease, etc. if required in the opinion of the primary investigator)
- Continue to monitor liver biochemistries at least twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic

During close observation, study drug can be continued, if desired, at the discretion of the Gilead Medical Monitor and the Principal Investigator.

If on-treatment elevations of ALT and/or AST exceed the values shown in Figure 7-2, are confirmed on repeat testing within 48-72 hours of results, and no alternative cause is immediately apparent, the subject must be placed into close observation and study drug must be withheld.

Figure 7-2. On-Treatment ALT/AST Monitoring Requiring Study Drug Withholding



* Unless subject has Gilbert's syndrome, in which case a direct bilirubin > 2 x baseline (average of screening & Day 1 values) will be used instead of total bilirubin.
**If not on therapeutic anticoagulation (e.g. warfarin). If on therapeutic anticoagulation, INR criteria is disregarded.

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

Subjects who develop signs or symptoms of liver toxicity (such as right upper quadrant discomfort, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%) which are suspected by the principal investigator to be drug-related, must have study drug withheld and be placed into close observation.

If study drug is withheld, it may be reintroduced with approval from the Medical Monitor if another etiology of elevated liver tests is identified. Study drug must be discontinued if close monitoring is not possible or if total bilirubin, ALT or AST elevation recurs following re-challenge with study drug. Subjects who discontinue study drug due to suspected hepatotoxicity must be followed until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels, until there is a satisfactory explanation for the changes observed, or for 3 months after drug discontinuation, whichever is longer.

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 AEs 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.

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

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 adverse events 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 with an AE 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 medication 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

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

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

Any premature termination of pregnancy (e.g., 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 Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the female 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

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

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

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

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

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE 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 objective of this study is as follows:

- To evaluate whether SEL can cause fibrosis regression and reduce progression to cirrhosis and associated complications in subjects with NASH and bridging (F3) fibrosis.

The secondary objective of this study is:

- To assess the safety and tolerability of SEL in subjects with NASH and bridging (F3) fibrosis.

The exploratory objectives of this study are as follows:

8.1.2. Primary Efficacy Endpoint

The primary efficacy endpoint at Week 48 includes the proportion of subjects 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).

8.1.3. Clinical Efficacy Endpoint

The clinical efficacy endpoint at Week 240 is EFS. EFS will be assessed by time to the first clinical event including progression to cirrhosis, liver decompensation events, liver transplantation, or all-cause mortality.

8.1.4. Secondary Endpoint

The secondary endpoints of this study are as follows:

- Proportion of subjects who have progression to cirrhosis by Week 48;
- Proportion of subjects who have a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 240;
- Proportion of subjects who have a ≥ 1-stage improvement in fibrosis at Week 48 and Week 240;
- Proportion of subjects who have NASH resolution without worsening of fibrosis at Week 48 and Week 240.

8.1.5. Exploratory Endpoints

CCI

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).

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

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

8.2.1.2. Safety

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

8.2.1.3. Pharmacokinetics

The PK analysis set will include all randomized subjects who took at least one dose of study drugs and for whom concentration data of analytes SEL (and its metabolite GS-607509 as applicable) are available. The PK of other SEL metabolites may be explored.

CCI [redacted]

8.2.1.4. 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.

8.3. Data Handling Conventions

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

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

Values for missing safety laboratory data 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 (i.e., 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.

8.4. Multiple Testing

When the primary histology efficacy endpoint is compared between each of the SEL arms and the placebo arm at Week 48, it will be tested at a two-sided 0.025 significance level to control an overall Type I error rate of 0.05 by Bonferroni adjustment.

The testing strategy for the clinical efficacy endpoint (EFS) is described below and is presented graphically in Figure 8-1.

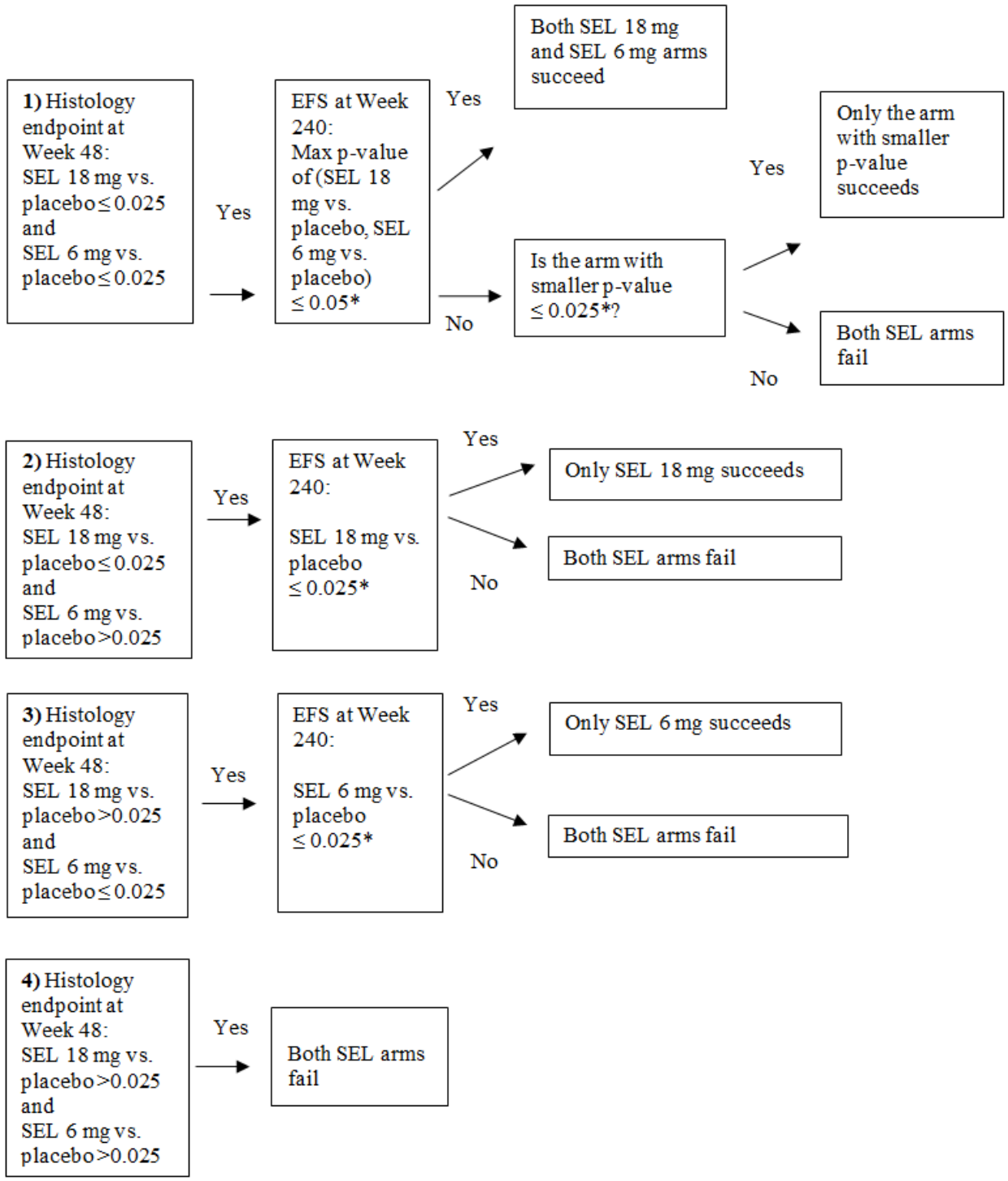
1) If the primary histology efficacy endpoint is significant in both SEL arms, the EFS endpoint will be tested for both SEL arms against placebo at Week 240 at a two-sided 0.05 significance level by the Hochberg procedure {Hochberg 1988}. If the larger p-value of SEL18 mg vs. placebo and SEL 6 mg vs. placebo is less than or equal to 0.05, the EFS endpoint for both SEL arms will be a success; if the larger p-value is > 0.05, the treatment arm with the larger p-value fails, and the smaller p-value will be compared with the significance level of 0.025 to determine the success of the treatment arm.

2) If the primary histology efficacy endpoint is significant in the SEL 18 mg but not the SEL 6 mg arm, the EFS endpoint will be tested for SEL 18 mg against placebo at Week 240 at a two-sided 0.025 significance level.

3) If the primary histology efficacy endpoint is significant in SEL 6 mg but not SEL18 mg arm, the EFS endpoint will be tested for SEL 6 mg against placebo at Week 240 at a two-sided 0.025 significance level.

4) If the primary histology efficacy endpoint is not significant in both the SEL 18 mg and SEL 6 mg arms, the trial will be terminated.

Figure 8-1. Multiple Testing Flow Chart



* Nominal alpha will be adjusted using Haybittle-Peto approach

Although no formal statistical inference on EFS is planned at the Week 48 analysis, the actual nominal significance level for the EFS endpoint at the Week 240 analysis will be adjusted using the Haybittle-Peto approach {Haybittle 1971}. The adjustment will be based on the number of events at both the Week 48 and Week 240 analyses, assuming an allocation of a two-sided significance level of 0.001 at the Week 48 analysis.

8.5. 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, and randomization stratification groups (presence or absence of diabetes; ELF™ score ≥ 9.76 or < 9.76), and other disease characteristic variables.

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

8.6. Efficacy Analysis

8.6.1. Primary Efficacy Endpoints Analysis

Primary Histology Efficacy Endpoint Analysis

A stratified MH test will be used to compare the differences in proportions of subjects who achieve a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 48 between each of the SEL arms and the placebo arm, adjusting for stratification factors. Subjects with missing data regarding fibrosis stage and NAS elements used to define worsening of NASH (hepatocellular ballooning and lobular inflammation) at Week 48 will be analyzed as treatment failures. The point estimates and 95% confidence intervals for the differences in proportions will be calculated.

Clinical Efficacy Endpoint Analysis

The clinical efficacy endpoint at Week 240 is EFS. EFS will be assessed by time to the first clinical event in the Randomized Phase. Differences in time to the first clinical events between each of the SEL arms and the placebo arm will be assessed using the stratified log-rank test. A sensitivity analysis of EFS that includes hepatic clinical events and liver-related death will also be performed. The clinical efficacy endpoint will only be evaluated at Week 240 for a SEL arm if the SEL arm demonstrates superiority over placebo for the primary efficacy endpoint at Week 48.

8.6.2. Secondary Efficacy Endpoint Analysis

A stratified MH test will be performed to compare the differences in proportions between the each of the SEL arms and the placebo arm adjusting for stratification factors for the following endpoints:

- Proportion of subjects who have progression to cirrhosis by Week 48;
- Proportion of subjects who have a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 240;
- Proportion of subjects who have a ≥ 1-stage improvement in fibrosis at Week 48 and Week 240;
- Proportion of subjects who have NASH resolution without worsening of fibrosis at Week 48 and Week 240.

8.6.2.1. Exploratory Endpoint Analyses

CCI [redacted]

8.7. Assessment of Noninvasive Measures of Fibrosis

Receiver operating characteristic (ROC) curves and measures of diagnostic test performance (e.g., sensitivity and specificity) will be used to determine whether baseline noninvasive measures of fibrosis and their change from baseline can predict histological regression and progression of fibrosis or the development of clinical complications.

8.8. Safety Analysis

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

All safety data collected on or after the date that SEL or PTM SEL was first dispensed up to the date of last dose of SEL or PTM SEL plus 30 days will be summarized by treatment group, including extent of exposure, adverse events, laboratory evaluations, and immunogenicity.

Safety data from the OL Phase will be summarized for overall subjects who roll-over into the OL Phase for safety review.

8.8.1. Extent of Exposure

Data for a subject's extent of exposure will be generated from the study drug administration eCRF. Exposure data will be summarized by treatment group and by study phase.

8.8.2. Adverse Events

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

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

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

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

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

8.8.3. 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 (refer to Appendix 4).

The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment-emergent.

8.8.4. Other Safety Evaluations

Vital sign measurements will be summarized by treatment arm and listed by subject.

8.9. Pharmacokinetic Analysis

SEL and GS-607509 plasma concentrations will be listed and summarized. CCI [redacted]

8.9.1. Exploratory Biomarker Analyses

CCI [redacted]

8.10. Sample Size

With a sample size of 320 subjects in each active treatment arm and 160 subjects in the placebo arm, the study has 94% of power to detect a difference in the proportion of subjects with a ≥ 1-stage improvement in fibrosis without worsening of NASH of 15% or more at Week 48 at a significance level of 0.025 (two-sided), assuming the proportion of subjects that meet the endpoint in the placebo arm is 12%.

With regard to the clinical efficacy endpoint, subjects will be followed for a period of up to 240 weeks. The estimate of the expected event rate is 30% in untreated patients, producing an expected EFS rate of 70% at 240 weeks in the placebo arm. SEL is expected to improve the EFS rate to 83.7% (expected event rate of 16.3%) compared with placebo (hazard ratio (HR), 0.50). We also expect a 20% overall dropout rate. Given the above assumptions, for comparison of each of the SEL arms versus the placebo arm, together with a total sample size of 800 subjects (2:2:1 ratio), and assuming the log-rank test statistic is evaluated using a two-sided 0.025 significance level, the study will have 85% power to evaluate the superiority of each SEL arm versus placebo with respect to EFS.

Therefore, the overall power for the trial, assuming independence between the primary efficacy endpoint and clinical efficacy endpoint, is 80% (94% x 85%). It should be noted that this is a lower bound estimate as these two endpoints are expected to be positively correlated.

8.11. Data Monitoring Committee

An external Data Monitoring Committee (DMC) that consists of three hepatologists and a PhD statistician will review the progress of the study, perform interim reviews of safety data, and provide recommendations to Gilead whether the nature, frequency, and severity of AEs

associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The initial meeting of the DMC will occur after 50 subjects have completed their Week 4 visit and approximately every 6 months thereafter to monitor the study for safety events.

The DMC's specific activities will be defined by a mutually agreed upon 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 GCP 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, as outlined in 21 the 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, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/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 or local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic 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 subject initials, date of birth, 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 investigator brochure, this protocol, eCRF, 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, i.e., 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 IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., 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. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data

verification within the electronic data capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF 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 (e.g., data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be sent to the designated disposal facility for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP that is destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences and its representatives, to the 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 agency(ies). 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.

After conclusion of the study and without prior written approval from Gilead Sciences, 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.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

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. The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g., attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, 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.

10. REFERENCES

Afzali A, Berry K, Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. Liver Transpl 2012;18 (1):29-37.

Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015;149 (2):389-97 e10.

Arthur JS, Ley SC. Mitogen-activated protein kinases in innate immunity. Nature reviews 2013;13 (9):679-92.

Canbay A, Friedman S, Gores GJ. Apoptosis: the nexus of liver injury and fibrosis. Hepatology 2004;39 (2):273-8.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Dietrich P, Hellerbrand C. Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. Best practice & research 2014;28 (4):637-53.

Dowman JK, Tomlinson JW, Newsome PN. Pathogenesis of non-alcoholic fatty liver disease. QJM 2010;103 (2):71-83.

Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44 (4):865-73.

Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up [Accepted Article]. Hepatology 2014.

Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61 (5):1547-54.

Faramawi MF, Wildman RP, Gustat J, Rice J, Abdul Kareem MY. The association of the metabolic syndrome with QTc interval in NHANES III. Eur J Epidemiol 2008;23 (7):459-65.

Feldstein AE, Wieckowska A, Lopez AR, Liu YC, Zein NN, McCullough AJ. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: A multicenter validation study. Hepatology 2009.

Gonzalez-Teran B, Matesanz N, Nikolic I, Verdugo MA, Sreeramkumar V, Hernandez-Cosido L, et al. p38gamma and p38delta reprogram liver metabolism by modulating neutrophil infiltration. EMBO J 2016;35 (5):536-52.

Hagstrom H, Nasr P, Ekstedt M, Kechagias S, Stal P, Bedossa P, et al. SAF score and mortality in NAFLD after up to 41 years of follow-up. Scand J Gastroenterol 2016:1-5.

Han MS, Jung DY, Morel C, Lakhani SA, Kim JK, Flavell RA, et al. JNK expression by macrophages promotes obesity-induced insulin resistance and inflammation. Science 2013;339 (6116):218-22.

Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Br J Radiol 1971;44 (526):793-7.

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75 (4):800-2.

Ichijo H, Nishida E, Irie K, ten Dijke P, Saitoh M, Moriguchi T, et al. Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways. Science 1997;275 (5296):90-4.

Imoto K, Kukidome D, Nishikawa T, Matsuhisa T, Sonoda K, Fujisawa K, et al. Impact of mitochondrial reactive oxygen species and apoptosis signal-regulating kinase 1 on insulin signaling. Diabetes 2006;55 (5):1197-204.

Kaufmann T, Jost PJ, Pellegrini M, Puthalakath H, Gugasyan R, Gerondakis S, et al. Fatal hepatitis mediated by tumor necrosis factor TNFalpha requires caspase-8 and involves the BH3-only proteins Bid and Bim. Immunity 2009;30 (1):56-66.

Kim YM, Kim TH, Kim YW, Yang YM, Ryu DH, Hwang SJ, et al. Inhibition of liver X receptor-alpha-dependent hepatic steatosis by isoliquiritigenin, a licorice antioxidant flavonoid, as mediated by JNK1 inhibition. Free Radic Biol Med 2010;49 (11):1722-34.

Kluwe J, Pradere JP, Gwak GY, Mencin A, De Minicis S, Osterreicher CH, et al. Modulation of hepatic fibrosis by c-Jun-N-terminal kinase inhibition. Gastroenterology 2010;138 (1):347-59.

Knebel B, Lehr S, Hartwig S, Haas J, Kaber G, Dicken HD, et al. Phosphorylation of sterol regulatory element-binding protein (SREBP)-1c by p38 kinases, ERK and JNK influences lipid metabolism and the secretome of human liver cell line HepG2. Arch Physiol Biochem 2014;120 (5):216-27.

Koek GH, Liedorp PR, Bast A. The role of oxidative stress in non-alcoholic steatohepatitis. Clin Chim Acta 2011;412 (15-16):1297-305.

Kotzka J, Knebel B, Haas J, Kremer L, Jacob S, Hartwig S, et al. Preventing phosphorylation of sterol regulatory element-binding protein 1a by MAP-kinases protects mice from fatty liver and visceral obesity. PLoS ONE 2012;7 (2):e32609.

Makie T, Nagai S, Sasakawa A, Kawamura K, Kuwahara T. Predicting tenofovir concentration on the basis of renal factors determined by routine tests. Am J Ther 2007;14 (6):514-8.

Nakagawa H, Hirata Y, Takeda K, Hayakawa Y, Sato T, Kinoshita H, et al. Apoptosis signal-regulating kinase 1 inhibits hepatocarcinogenesis by controlling the tumor-suppressing function of stress-activated mitogen-activated protein kinase. Hepatology 2011;54 (1):185-95.

Nakagawa H, Maeda S, Hikiba Y, Ohmae T, Shibata W, Yanai A, et al. Deletion of apoptosis signal-regulating kinase 1 attenuates acetaminophen-induced liver injury by inhibiting c-Jun N-terminal kinase activation. Gastroenterology 2008;135 (4):1311-21.

Neuschwander-Tetri BA. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: the central role of nontriglyceride fatty acid metabolites. Hepatology 2010;52 (2):774-88.

Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385 (9972):956-65.

Nieto N. Oxidative-stress and IL-6 mediate the fibrogenic effects of [corrected] Kupffer cells on stellate cells. Hepatology 2006;44 (6):1487-501.

Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. Clin Liver Dis 2007;11 (1):1-16, vii.

Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-alpha and -delta, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. Gastroenterology 2016;150 (5):1147-59 e5.

Rolo AP, Teodoro JS, Palmeira CM. Role of oxidative stress in the pathogenesis of nonalcoholic steatohepatitis. Free Radic Biol Med 2012;52 (1):59-69.

Sabio G, Davis RJ. TNF and MAP kinase signalling pathways. Seminars in immunology 2014;26 (3):237-45.

Sumida Y, Niki E, Naito Y, Yoshikawa T. Involvement of free radicals and oxidative stress in NAFLD/NASH. Free radical research 2013;47 (11):869-80.

Takeda K, Noguchi T, Naguro I, Ichijo H. Apoptosis signal-regulating kinase 1 in stress and immune response. Annu Rev Pharmacol Toxicol 2008;48:199-225.

Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol 2016;65 (3):589-600.

The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. . Health Policy 1990;16 (3):199-208.

Tobiume K, Saitoh M, Ichijo H. Activation of apoptosis signal-regulating kinase 1 by the stress-induced activating phosphorylation of pre-formed oligomer. Journal of cellular physiology 2002;191 (1):95-104.

Vallerie SN, Hotamisligil GS. The role of JNK proteins in metabolism. Science translational medicine 2010;2 (60):60rv5.

Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34 (3):274-85.

Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60 (2):715-35.

Voulgari C, Tentolouris N, Papadogiannis D, Moyssakis I, Perrea D, Kyriaki D, et al. Increased left ventricular arrhythmogenicity in metabolic syndrome and relationship with myocardial performance, risk factors for atherosclerosis, and low-grade inflammation. Metabolism: clinical and experimental 2010;59 (2):159-65.

Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011;140 (1):124-31.

Win S, Than TA, Min RW, Aghajan M, Kaplowitz N. c-Jun N-terminal kinase mediates mouse liver injury through a novel Sab (SH3BP5)-dependent pathway leading to inactivation of intramitochondrial Src. Hepatology 2016;63 (6):1987-2003.

Wissing ER, Boyer JG, Kwong JQ, Sargent MA, Karch J, McNally EM, et al. P38alpha MAPK underlies muscular dystrophy and myofiber death through a Bax-dependent mechanism. Human molecular genetics 2014;23 (20):5452-63.

Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 2014;59 (6):2188-95.

Xie Y, Ramachandran A, Breckenridge DG, Liles JT, Lebofsky M, Farhood A, et al. Inhibitor of apoptosis signal-regulating kinase 1 protects against acetaminophen-induced liver injury. Toxicol Appl Pharmacol 2015;286 (1):1-9.

Yeh MM, Brunt EM. Pathological features of fatty liver disease. Gastroenterology 2014;147 (4):754-64.

Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64 (1):73-84.

Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011;53 (6):1874-82.

11. APPENDICES

Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib in Subjects with Nonalcoholic Steatohepatitis (NASH) and Bridging (F3) Fibrosis

GS-US-384-1943, Amendment 2, 31 May 2018

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

PPD

PPD

Signature

31 May 2018

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 Tables

Study Procedures Table – Screening to Week 48

Assessments	Screening	Day 1[a]	On-treatment Visits												
			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														
Medical History	X														
Physical Examination	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Vital Signs including Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Waist Circumference	X	X		X		X			X						X
12-lead ECG	X														
CP/MELD Scores[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Ascites and Hepatic Encephalopathy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver Biopsy[d]	X														X
Abdominal Ultrasound (OL Phase only)		X							X						X
Elastography (if available)	X[e]	X[f]							X						X

Assessments	Screening	Day 1[a]	On-treatment Visits												
			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
Health Related Quality of Life Questionnaires[g]		X				X			X						X
Health Resource Utilization Questionnaires[g]		X				X			X						X
Stool Frequency Assessment		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
Adverse Events	X[h]	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
Dispense Study Drug		X		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
Laboratory Assessments															
Subject Fasting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[i], Hematology, Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Insulin and Lipids		X		X		X			X						X
HbA1c	X	X		X		X			X						X
eGFR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[j]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Single PK Sampling		X[l]	X[k]	X[k]	X[l]	X[k]	X[l]	X[l]	X[k]	X[l]	X[l]	X[l]	X[l]	X[l]	X[k]

Assessments	Screening	Day 1[a]	On-treatment Visits												
			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
Blood Collection (Biomarkers)	X	X				X			X						X
Urine Collection		X				X			X						X
Urine Drug Screen	X														
HIV-1, HBV, HCV Serology	X														
CCI															
CCI															
Approximate amount of blood drawn (mL)[n]	70	65	15	15	12	60	12	12	60	12	12	12	12	12	65

Study Procedures Table – Week 60 to Follow Up

Assessments	On-treatment Visits										Follow Up[o]	Telephone Follow-Up[p]
	Week 60	Week 72 / Week 168	Week 84 / Week 180	Week 96 / Week 192	Week 108 / Week 204	Week 120 / Week 216	Week 132 / Week 228	Week 144 / Week 240 (EOT)	Week 156	ET[o]		
Physical Examination	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Vital Signs including Body Weight	X	X	X	X	X	X	X	X	X	X	X	
Waist Circumference		X		X		X		X		X		
Liver Biopsy[d]								X[q]		X[r]		
CP/MELD scores[c]	X	X	X	X	X	X	X	X	X	X		
Assess Ascites and Hepatic Encephalopathy	X	X	X	X	X	X	X	X	X	X		
Abdominal Ultrasound (OL Phase only)		X		X		X		X		X		
Elastography (if available)				X				X		X		
Health Related Quality of Life Questionnaires[g]		X		X		X		X		X		
Health Resource Utilization Questionnaires[g]		X		X		X		X		X		
Stool Frequency Assessment	X	X	X	X	X	X	X	X	X	X	X	
Lifestyle Modification Counseling	X	X	X	X	X	X	X	X	X	X		
Adverse Events	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	
Dispense Study Drug	X	X	X	X	X	X	X	X[s]	X			
Review of Study Drug Dosing Compliance (Pill Count)	X	X	X	X	X	X	X	X	X	X		

Assessments	On-treatment Visits										Follow Up[o]	Telephone Follow-Up[p]
	Week 60	Week 72 / Week 168	Week 84 / Week 180	Week 96 / Week 192	Week 108 / Week 204	Week 120 / Week 216	Week 132 / Week 228	Week 144 / Week 240 (EOT)	Week 156	ET[o]		
Laboratory Assessments												
Subject Fasting	X	X	X	X	X	X	X	X	X	X	X	
Chemistry[i], Hematology, Coagulation	X	X	X	X	X	X	X	X	X	X	X	
Insulin and Lipids		X		X		X		X		X		
HbA1c		X		X		X		X		X		
eGFR	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Testing[j]	X	X	X	X	X	X	X	X	X	X	X	
Single PK sampling[l]	X	X	X	X	X	X	X	X	X	X[t]		
Blood Collection (Biomarkers)				X				X		X		
Urine Collection				X				X		X		
CCI [redacted]												
Approximate amount of blood drawn (mL)[n]	12	15	12	65	12	15	12	65	12	65	10	

a Subjects starting the OL Phase of the study will complete the same study procedures as during the Randomized Phase of the study, starting with the Day 1 visit
b Symptom-driven PE
c CP score to be calculated only at Screening
d Not to be performed during the OL Phase of the study
e CCI [redacted]
f CCI [redacted]
g For subjects with questionnaires available at Day 1
h Adverse Events reporting during Screening is limited to serious adverse events and adverse events related to study procedures
i Additional testing: digoxin level at Day 1 and Week 1 and as needed in subjects taking digoxin (refer to Section 5.4) and CPK level for subjects in close observation for DILI (refer to Section 7.5)
j Females of childbearing potential only (refer to Appendix 3). Serum pregnancy test at Screening and urine pregnancy test at Day 1 and every 4 weeks thereafter. Starting at the Week 48 visit, urine pregnancy testing kits will be provided for home testing every 4 weeks, between in-clinic study visits. All females of childbearing potential will be contacted every 4 weeks and asked to report the result of the urine pregnancy tests. FSH testing as per Appendix 3

k To be performed during the Randomized Phase in all subjects and during the OL Phase, only in subjects with severe hepatic impairment (Child-Pugh Class C) in combination with renal impairment (eGFR < 30 mL/min)
l To be performed during the OL Phase, only in subjects with severe hepatic impairment (Child-Pugh Class C) in combination with renal impairment (eGFR < 30 mL/min)
m CCI [redacted]
n For specific blood volumes at each visit, please refer to the current approved ICF
o Subjects prematurely discontinuing from the study should complete an ET visit within 30 days of last dose, Follow-Up visit 4 weeks later and a Telephone Follow-Up visit after the ET visit
p To be performed 12 weeks after the Week 240/EOT or ET visit. At the discretion of the investigator, an unscheduled visit may be completed if the subject reports abnormal or concerning symptoms
q Not to be performed at the Week 144 visit
r To be performed at the discretion of the investigator
s Not to be performed at the Week 240/EOT visits
t To be collected in all subjects that ET in Randomized or OL Phase

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

1) Definitions

a) Definition of Childbearing Potential

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

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

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

b) Definition of Male Fertility

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

Preclinical and clinical drug-drug interaction (DDI) data indicate that SEL is unlikely to alter the exposure of hormonal contraceptives through induction of human drug metabolizing enzymes or drug transporters. Please refer to the latest version of the IB 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 Day 1 visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. Female subjects must agree to one of the following from Screening until 30 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

  — 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)

  The above described methods are considered preferred methods of highly effective contraception in this protocol.

- 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:

  Hormonal methods (each method *must* be used with a condom in the male partner):

  — 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.

* Not approved in Japan

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 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 30 days after the last dose of study drug. Female partners of male study subjects are asked to select one of the above methods.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., 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 30 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 or within 30 days of last study drug 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. Common Terminology Criteria for Adverse Events (CTCAE)

Refer to the Study Reference Binder for additional CTCAE information.

Appendix 5. West Haven Criteria

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

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

Adapted from {Vilstrup 2014}