CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-0976 in Subjects with Nonalcoholic Steatohepatitis	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	124915	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	Not Available	
Indication:	Nonalcoholic steatohepatitis (NASH)	
Protocol ID:	GS-US-426-3989	
Gilead Sciences Medical Monitor	Name: Telephone: Fax: Email:	PPD PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1:	20 June 2016 15 December 2016

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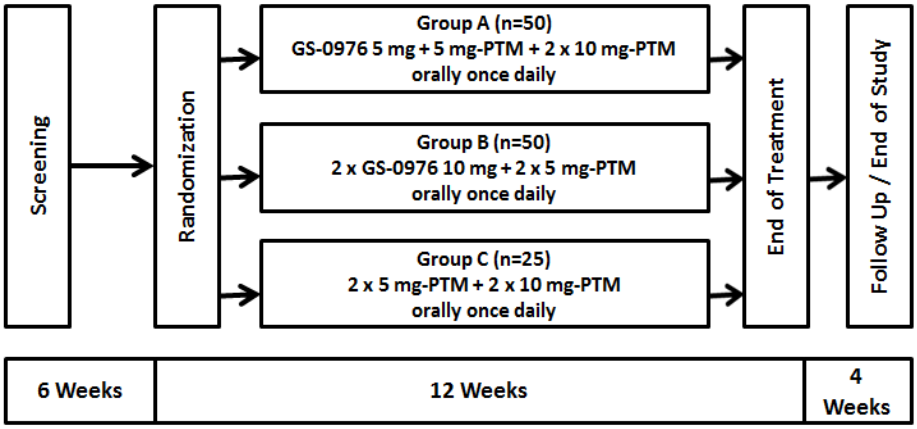
PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-0976 in Subjects with Nonalcoholic Steatohepatitis
IND Number:	124915
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	Not Available
Study Centers Planned:	Approximately 50 centers in the United States
Objectives:	The primary objective of this study is to evaluate the safety and tolerability of GS-0976 in subjects with nonalcoholic steatohepatitis (NASH) as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and magnetic resonance elastrography (MRE) or a historical liver biopsy consistent with NASH and non-cirrhotic fibrosis. The exploratory objectives of this study are listed in Section 2.
Study Design:	This is a Phase 2 randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and biological activity of GS-0976 in subjects with NASH as assessed by MRI-PDFF and MRE, or a historical liver biopsy consistent with NASH and non-cirrhotic fibrosis. Participation in the study can last up to approximately 22 weeks, which includes a 6-week Screening period, a 12-week treatment period during which study drugs will be administered, and a 4-week follow-up period. The screening period may be extended under special circumstances with the explicit approval of the Medical Monitor. 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:



Study drugs will be administered for a total of 12 weeks. Randomization will be stratified by the presence or absence of diabetes mellitus as determined by medical history, use of medication for indication of diabetes mellitus, or based on Screening lab values if previously undiagnosed (i.e., hemoglobin A1c ≥ 6.5% OR fasting plasma glucose ≥ 126 mg/dL).

Number of Subjects Planned:

Approximately 125 subjects

Target Population:

Males and non-pregnant, non-lactating females between 18-75 years of age without cirrhosis and with NASH as assessed by MRI-PDFF and MRE or a historical liver biopsy consistent with NASH and non-cirrhotic fibrosis.

Duration of Treatment:

Subjects will be treated for 12 weeks.

Diagnosis and Main Eligibility Criteria:

Key inclusion and exclusion criteria are as follows:

Key Inclusion Criteria:

- Meets the following conditions:

a) A clinical diagnosis of nonalcoholic fatty liver disease (NAFLD) with imaging or a liver biopsy documenting fatty liver within two years prior to Screening (if necessary, an ultrasound may be performed during Screening to confirm NAFLD), and

b) Screening MRI-PDFF with ≥ 8% steatosis, and

c) Screening MRE with liver stiffness ≥ 2.5 kPa.

Note: criterion a. must be met before evaluating criteria b. and c.

OR

- A historical liver biopsy within 12 months of Screening consistent with NASH (defined as the presence of steatosis, lobular inflammation, and hepatocellular ballooning) with fibrosis, but not cirrhosis, and
- No documented weight loss > 5% between the date of the liver biopsy and Screening.
- Platelet count ≥ 100,000/mm^3
- Creatinine Clearance (CL_{cr}) as calculated by the Cockcroft-Gault equation ≥ 60 ml/min

Key Exclusion Criteria:

- Pregnant or lactating females;
- ALT > 5 x ULN;
- Other causes of liver disease including autoimmune, viral, and alcoholic liver disease;
- Cirrhosis of the liver as defined by any of the following:

a) Cirrhosis on historical liver biopsy (e.g. NASH CRN classification stage 4 or equivalent);

b) Evidence of cirrhosis on liver imaging (e.g. ultrasound, CT, or MRI) including a nodular liver surface, splenomegaly, or portal venous collaterals;

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

d) Screening FibroSURE/FibroTest® ≥ 0.75, unless a historical liver biopsy within 12 months of Screening does not reveal cirrhosis. In patients with Gilbert's syndrome or hemolysis, FibroSURE/FibroTest® will be calculated using direct bilirubin instead of total bilirubin.

- BMI < 18 kg/m^2;
- INR > 1.2, unless on anticoagulant therapy;
- Total bilirubin > 1 x ULN, except with diagnosis of Gilbert's syndrome;

Refer to Sections 4.2 and 4.3 for complete listing of inclusion and exclusion criteria.

Subjects with laboratory abnormalities outside of the above parameters may be approved for inclusion in the trial with approval from the Medical Monitor.

Study Procedures/ Frequency:

After signing the informed consent form, subjects will complete a Screening visit which will include the following assessments: complete medical history, physical examination (PE), vital signs, laboratory assessments (blood chemistry, hematology, coagulation panel, hemoglobin A1c, and HIV-1, HBV, and HCV serology), serum pregnancy test (for females of child-bearing potential), urine drug test, standard 12-lead ECG, ultrasound (if necessary), review of adverse events, concomitant medications, and MRI-PDFF and MRE examinations.

After the Screening period and a randomization visit at Baseline/Day 1, study visits will occur on Weeks 1, 4, 8, 12, and a Follow-Up visit 4 weeks after the last dose of study drugs. At minimum, vital signs, symptom driven PE, safety laboratory tests (blood chemistry, hematology, coagulation panel, and lipid profile), review of adverse events and concomitant medications will be done at every visit.

Eligible subjects will be randomized to one of 3 treatment groups. Prior to initial dosing, required Baseline/Day 1 assessments will be performed and will include symptom driven PE, vital signs (including waist circumference), laboratory assessments, pregnancy tests (for females of child-bearing potential), urine, blood, and stool collection for biomarker assessment, Quality of Life (QoL) questionnaires, standard 12-lead ECG, FibroScan® (if available), review of adverse events and concomitant medications.

CCI [redacted]

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

- MRE and MRI-PDFF at Week 12
- FibroScan® at Baseline/Day 1 and Week 12 (if available)
- Single PK sampling at Weeks 1, 4, 8, and 12
- Blood collection for Biomarkers at Baseline/Day 1, and at Weeks 1, 4, and 12
- Urine collection for Biomarkers at Baseline/Day 1, and at Weeks 1, 4, and 12
- 12-lead ECGs at Baseline/Day 1 and Week 12
- Hematology, blood chemistry, fasting lipid profile, PT, PTT, and INR at Baseline/Day 1, and at Weeks 1, 4, 8, 12, and Follow-Up visit
- Hemoglobin A1c (HbA1c) at Baseline/Day 1 and Week 12
- Stool collection for Biomarkers at Baseline/Day 1 and Week 12

	• Urine pregnancy test (females of childbearing potential only) at Baseline/Day 1, and at Weeks 4, 8, 12, and Follow-Up visit • SF-36, WPAI, and CLDQ at Baseline/Day 1 and Week 12 Subjects will return for their final visit, the Follow-Up visit, 4 weeks after the last dose of study drugs. At this visit assessments include a symptom driven PE, vital signs, review of concomitant medications and AEs, and safety laboratory tests. A urine pregnancy test will be performed for females of child bearing potential only. CCI [redacted]
Test Product, Dose, and Mode of Administration:	• Treatment Group A: GS-0976 5 mg (1 x 5 mg capsule, 1 x 5 mg-PTM capsule, 2 x 10 mg-PTM capsules) administered orally once daily; n=50 subjects • Treatment Group B: GS-0976 20 mg (2 x 10 mg capsule, 2 x 5 mg-PTM capsules) administered orally once daily; n=50 subjects • Treatment Group C: GS-0976 Placebo (2 x 5 mg-PTM capsules, 2 x 10 mg-PTM capsules) administered orally once daily; n=25 subjects
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-match 5 mg (5 mg-PTM) GS-0976 capsules and placebo-to-match 10 mg capsules (10 mg-PTM) are identical in size, shape, color and appearance to their corresponding strengths of active GS-0976 capsules.
Criteria for Evaluation:	
Safety:	The primary endpoint is the safety of GS-0976 in subjects with NASH. 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. An independent, external Data Monitoring Committee (DMC) that consists of two hepatologists and a PhD statistician will convene once 20 subjects have been randomized and every 3 to 4 months thereafter to monitor the study for safety events. The DMC will meet on an ad hoc basis if there are at least 3 similar Grade $\geq$ 3 serious, treatment related Common Terminology Criteria for Adverse Events (CTCAE) observed in the trial. In the event of two similar Grade 4-CTCAE treatment related

	events or one Grade 5-CTCAE treatment related event, the DMC will review the data and advise the sponsor regarding stopping or continuing the trial.
Efficacy:	Efficacy will be assessed through a number of exploratory endpoints. These exploratory endpoints are described in Section 8.1.3.
Pharmacokinetics:	A single PK blood sample will be collected at each on-treatment visit for all subjects. Plasma concentrations of GS-0976, and other metabolites as appropriate, will be determined for PK analyses as applicable.

Statistical Methods:

Safety Analysis:	All safety data collected will be listed and summarized, as appropriate, by treatment group.
Efficacy Analysis:	The biological activity of GS-0976 will be evaluated using biomarker variables. Because efficacy endpoints will be evaluated for exploratory purpose, formal statistical comparisons will not be made for these endpoints. Ninety-five percent confidence intervals (95% CI) will be provided if applicable.
Exploratory Analysis:	Point estimates and 95% CI will be calculated for all continuous exploratory parameters (e.g. MRI-PDFF, MRE, FibroScan®). For categorical variables, descriptive statistics will be calculated with count and percentage of subjects in each category by treatment group.
Sample Size:	Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof of concept studies.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
ACC	acetyl-CoA carboxylases
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo B	apolipoprotein B
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time 0 to the last measurable concentration
AUC_{inf}	area under the plasma/serum/PBMC concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-last}} + (Clast/\lambda_z)$
$AUC_{partial}$	partial area under the plasma/serum concentration versus time curve
AUC_{tau}	area under the plasma/serum/PBMC concentration versus time curve over the dosing interval
AUROC	area under the receiver operating characteristic curve
BAP	Biomarker Analysis Plan
BID	twice a day
BMI	body mass index
BUN	blood urea nitrogen
BW	body weight
C4	7-alpha-hydroxy-4-cholesten-3-one
CFR	Code of Federal Regulations
CI	confidence interval
CK-18	cytokeratin 18
CLDQ	Chronic Liver Disease questionnaire
CL/F	apparent oral clearance
CL_{cr}	creatinine clearance
CL_{renal}	Renal clearance
C_{last}	last observed quantifiable serum/plasma/PBMC concentration of the drug
C_{max}	maximum observed concentration of drug
C_{min}	minimum observed plasma/serum concentration of drug
CRO	contract (or clinical) research organization
CSR	clinical study report
CT	computed tomography
C_{tau}	observed drug concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450

CYP3A	cytochrome P4503A
DILI	drug induced liver injury
dL	deciliter
DMC	Data Monitoring Committee
DNL	de novo lipogenesis
DSPH	Drug Safety and Public Health
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
ELF™ Test	enhanced liver fibrosis test
ESA	erythropoiesis-stimulating agent
eSAE	electronic serious adverse event
eSSR	electronic special situations report
ET	early termination
EU	European Union
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FGF19	fibroblast growth factor 19
FSH	follicle stimulating hormone
GCP	Good Clinical Practice (Guidelines)
GCSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
Hct	hematocrit
HCV	hepatitis C virus
HCV Ab	hepatitis C antibody
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HLGT	high-level group term
HLT	high-level term
HOMA-IR	homeostatic assessment of insulin resistance
HRQoL	health related quality of life
IB	Investigator Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IEC	independent ethics committee/ institutional ethics committee
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
kg	kilogram
LDH	lactate dehydrogenase
LLT	lower-level term
MAD	multiple ascending dose
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
miRNA	micro ribonucleic acid
mmHg	millimeters of mercury
MPR	metabolite-to-parent
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NMR	nuclear magnetic resonance spectroscopy
NOEL	no-observed--effect-level
NOAEL	no observed adverse event level
N/C	not calculated
OATP	organic anion-transporting polypeptide
oz	ounce
PE	physical exam
PG	pharmacogenomics(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PT	preferred term
PT	prothrombin time
PTM	placebo-to-match
PTT	partial prothrombin time
QD	once daily
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
RAUC	Ratio of Day 10 $AUC_{0\text{-}tau}$ / Day 1$AUC_{0\text{-}t}$
RBC	red blood cell count
RNA	ribonucleic acid
ROS	reactive oxygen species
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SF-36	Short Form (36) Health Survey
SOC	System Organ Class
SOP	standard operating procedure
SSR	special situations report
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
T_{max}	the time (observed time point) of C_{max}
$T_{1/2}$	an estimate of the terminal elimination half-life of the drug in, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TPO	Thrombopoietin
ULN	Upper limit of the normal range
US	United States
Vz/F	apparent volume of distribution of the drug
WBC	White blood cell count
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

1. INTRODUCTION

1.1. Background

Chronic liver disease and the consequences of end-stage liver disease are increasing globally despite improved prevention and treatment of viral hepatitis. This is due to the emerging epidemics of obesity, metabolic syndrome, and diabetes mellitus that are leading to an increased incidence of nonalcoholic fatty liver disease (NAFLD). Nonalcoholic fatty liver disease is characterized by the excess accumulation of lipid droplets within the liver, also known as hepatic steatosis. Prevalence rates of NAFLD range from 6% to 37% worldwide {Ong 2007, Vernon 2011}. Nonalcoholic steatohepatitis (NASH), an aggressive form of NAFLD characterized by the presence of inflammation and hepatocellular ballooning, with or without fibrosis, is present in approximately 25% of patients with NAFLD. Nonalcoholic steatohepatitis is associated with increased liver-related mortality {Ong 2007, Williams 2011}. In the United States (US), it has been estimated that 3% to 6% of the population, {Vernon 2011, Wanless 1990}, or the equivalent of up to 15 million adults, have NASH. NASH represents a significant and growing unmet medical need for which there are no currently approved therapies. Furthermore, as NASH is a manifestation of the metabolic syndrome, risk factors for cardiovascular disease (eg, atherosclerotic disease, cardiac arrhythmogenicity) frequently coexist in these patients {Dietrich 2014, Faramawi 2008, Voulgari 2010}. A treatment that targets the underlying metabolic disorder could potentially ameliorate these cardiovascular risks and associated morbidity and mortality.

Nonalcoholic steatohepatitis is primarily thought to occur as the result of the metabolic syndrome, the impact of obesity, insulin resistance, and dyslipidemia in the liver. Simple steatosis is not sufficient to cause liver injury; it is the presence of inflammation and hepatocellular injury on the background of steatosis that defines NASH and results in the progression to end-stage liver disease and its complications. The “2-hit” hypothesis of NASH suggests that in the setting of steatosis and metabolic dysfunction, increased oxidative stress and the generation of reactive oxygen species (ROS) likely mediate the inflammatory changes in the liver (steatohepatitis) that may lead to progressive fibrosis {Dowman 2010, Kannel 1982, Koek 2011, Sumida 2013}. The major pathways in NASH disease progression include those involved in metabolic dysfunction in the hepatocyte, and activation of hepatic stellate cells and macrophages leading to progressive inflammation and liver fibrosis. Advanced fibrosis and cirrhosis are characterized by extensive collagen deposition and remodeling of the extracellular matrix. In addition, evidence suggests that lipotoxic intermediates of fatty acids likely contribute to the etiology of NASH {Neuschwander-Tetri 2010}.

Over time, NASH may result in progressive liver fibrosis, ultimately leading to cirrhosis in 10-20% of affected patients. Advanced fibrosis (bridging fibrosis or cirrhosis) is associated with increased morbidity and mortality {Ekstedt 2015, Yeh 2014}. Patients with cirrhosis may develop hepatocellular carcinoma (HCC) and other complications of end-stage liver disease, including jaundice, fluid retention (edema and ascites), portal hypertension and variceal bleeding, impaired coagulation and hepatic encephalopathy. Decompensated liver disease, as

defined by the development of one of the above complications, has a high mortality and the only known effective treatment is liver transplantation. With the increasing prevalence of obesity and obesity-related diseases, NASH is expected to become the leading indication for liver transplantation, and the leading etiology of HCC among liver transplant recipients in the US {Afzali 2012, Wong 2014}.

1.2. GS-0976

GS-0976 is a small molecule allosteric inhibitor that acts at the protein-protein homodimer interface of acetyl coenzyme A (acetyl-CoA) carboxylases (ACC) ACC1 and ACC2, to prevent dimerization. ACC1 and ACC2 are important regulators of fatty acid metabolism. ACC1 catalyzes the first step of de novo lipogenesis (DNL) by converting acetyl-CoA to malonyl-CoA while ACC2 regulates the entry of fatty acids into the mitochondria where beta oxidation can occur. Therefore, inhibition of ACC1 and ACC2 will reduce DNL and increase fatty acid beta oxidation. GS-0976 is being developed for the treatment of NASH.

1.2.1. General Information

For further information on GS-0976, refer to the current Investigator Brochure (IB) for GS-0976.

1.2.2. Nonclinical Pharmacology

GS-0976 has been characterized in several biochemical and cellular assays to enhance the understanding of the mechanism of action and has been well characterized in vivo in several mechanistic models to demonstrate target engagement and in animal disease models to demonstrate specific activity on endpoints relevant to metabolic disease. Moreover, extensive safety pharmacology and receptor screening studies have been conducted.

The results of these pharmacodynamic (PD) studies indicate that GS-0976 can favorably affect the DNL, hepatic steatosis, insulin resistance, and body weight/body fat elevations produced in nonclinical models of metabolic disease without affecting food consumption or markers of liver function. In total, these studies confirm the potential for GS-0976 to impact important metabolic endpoints associated with NASH.

1.2.3. Nonclinical Toxicology

The toxicity of GS-0976 was evaluated in rats and dogs in acute and repeated dose nonclinical studies up to 13 weeks in duration. Selection of the test species was based on the in vitro and in vivo assessment of metabolism. In in vitro experiments using human hepatocytes, no human-specific metabolites were identified and all metabolites detected were also present in rat and/or dog hepatocytes.

There were no adverse findings in safety pharmacology studies (central nervous system, respiratory and cardiovascular studies) at exposures ~ 50 fold above the predicted steady-state clinical exposure (C_{max} ~110 ng/mL) after administration of 20 mg GS-0976 once daily (QD) fasted. The genotoxicity potential of GS-0976 was considered low as the compound is negative in the in vitro Ames, chromosome aberration studies and the in vivo mouse micronucleus study.

Single doses of GS-0976 up to 1000 mg/kg were tolerated in rats and dogs. In the 28-day studies, the no-observed-adverse-effects levels (NOAELs) for the rat and dog were 60 and 100 mg/kg/day respectively, the highest doses tested in the studies, affording exposure margins of at least 23 (rat) and 63 (dog) times above the predicted steady-state clinical exposure after administration of 20 mg GS-0976 QD fasted (240 ng•h/mL). In the 13-week rat study, no dose limiting toxicity was observed and the NOAEL was 60 mg/kg/day, the highest dose tested, providing an exposure margin of 23-fold above predicted steady-state clinical exposure. In the 13-week dog study, bilateral posterior cortical cataracts and histological evidence of cataracts were observed at 90 mg/kg/day, with progression in severity after a 28-day recovery period. There was no evidence of cataracts at doses ≤ 30 mg/kg/day. In the 13-week dog study, the presence of cataracts was found at exposures approximately 82 times above the predicted steady-state clinical exposure. No evidence of cataracts was observed at doses ≤ 30 mg/kg/day. The NOAEL for the 13-week dog study was 30 mg/kg/day, providing an exposure margin of approximately 15 fold above the predicted steady-state clinical exposure at 20 mg.

In the rat embryo-fetal development dose-range finding study, maternal toxicity and fetal abnormalities (external and soft tissue malformations, and developmental variations) were observed at doses ≥ 50 mg/kg/day in a dose-dependent manner. The no-observed-effect level (NOEL) for the embryo-fetal rat study was 25 mg/kg/day at an approximate exposure margin of 5.8 times above the predicted steady-state clinical exposure. In the rabbit study, 100 mg/kg/day was not tolerated and maternal toxicity (decreased body weight gain and food consumption) was observed at doses ≥ 25 mg/kg/day. While decreases in fetal weights were observed at doses ≥10 mg/kg/day, no external malformations and developmental variations were observed at all doses. The NOEL for the embryo-fetal rabbit study was less than 10 mg/kg/day. At this dose, the predicted steady-state clinical exposure margin is approximately 53. The observed embryo-fetal effects were not unexpected as the deletion of ACC1 in mice is embryonically lethal.

1.2.4. Nonclinical Pharmacokinetics

GS-0976 is highly protein bound in plasma, and the volume of distribution of GS-0976 across nonclinical species is greater than total body water (0.7 L/kg), suggesting that GS-0976 is well distributed. A significant fraction of the absorbed parent compound is extracted by the liver indicating that GS-0976 is available to the target site (ie, the liver).

The metabolism of GS-0976 has been evaluated in in vitro incubations of rat, dog, Cynomolgus monkey, and human hepatocytes. No metabolites unique to the human were detected. In vivo metabolite identification studies in Sprague-Dawley rat and Beagle dog have demonstrated that the primary metabolite of GS-0976 is the glucuronide conjugate.

Neither GS-0976 nor the metabolite, NDI-011535, inhibits the cytochrome P450 (CYP) enzymes involved in drug metabolism. GS-0976 is not an inducer of CYP1A2 or CYP2B6 isozymes and is a mild inducer of CYP 3A4 in human hepatocytes in vitro.

A single nonclinical study to evaluate elimination of GS-0976 and the metabolite NDI-011535 was performed in bile duct cannulated Sprague-Dawley rats to profile concentrations over time in plasma, urine, and bile. Overall, the pharmacokinetic (PK) profile in plasma and bile indicate that GS-0976 is rapidly cleared from the plasma compartment, and the primary route of elimination is via the bile.

1.2.5. Clinical Trials of GS-0976

1.2.5.1. Study 0976-101: Single Ascending Dose (SAD) Study

The first-in-human single ascending dose (SAD) study (Protocol Number 0976-101) was a randomized, placebo-controlled, double-blind study performed in normal, healthy adult subjects at one study center in the United States with a starting dose of 30 mg. The dosing in this study is completed with PK and tolerability data obtained following dosing of 30, 80, 200, 500, 800, and 1000 mg in the fasted state and 200 mg following a high fat meal (fed state) to cohorts of 8 subjects (6 active and 2 placebo control per group). Final data from the SAD study indicated that single doses of GS-0976 were tolerated across the dose range of 30 to 1000 mg. There were no deaths, serious adverse events (SAEs), or subject discontinuations due to adverse events (AEs) in this study. There were no clinically important treatment related or dose related trends in the incidence or severity of treatment emergent adverse events (TEAEs), clinical laboratory, vital sign, ECG, or physical examination assessments in this study. Abdominal discomfort, vessel puncture site pain, dizziness, and presyncope, reported by 2 subjects each (6% overall for fasted GS-0976), were the most frequently reported events in this study. Of the 27 TEAEs reported in the study, all were of Grade 1 severity. The principal investigator considered 2 TEAEs to be probably related (1 episode each of nausea and dyspepsia in placebo fasted subjects), 4 possibly related (1 episode of cough in the 30 mg GS-0976 fasted group and 1 episode each of discolored feces, abdominal discomfort, and diarrhea in the 500 mg GS-0976 fasted group), and 21 unrelated to study treatment.

Pharmacokinetic parameters of GS-0976 are presented in Table 1-1. Plasma GS-0976 maximum plasma concentration (C_{max}) and overall exposure (AUC_{inf}) generally increased in a dose proportional manner across the range of 30 to 500 mg, under fasted conditions, with greater than dose-proportional increases above 500 mg. Similar results were observed for plasma NDI-011535 (glucuronide metabolite of GS-0976). The apparent total body clearance (CL/F) and apparent volume of distribution (V_z/F) of GS-0976 decreased with increasing GS-0976 doses of 800 mg and 1000 mg. Urinary excretion of unchanged GS-0976 was negligible. GS-0976 C_{max} was approximately 68% lower under fed compared to fasted conditions; however, overall plasma GS-0976 exposure (based on AUC_{0-t} and AUC_{0-inf}) was only approximately 9% to 14% lower under fed compared to fasted conditions, which may not be a clinically significant difference. The median T_{max} and mean $T_{1/2}$ values were similar under fed and fasted conditions, although there was a delay in the first quantifiable concentration and a prolonged absorption/distribution phase observed under fed compared to fasted conditions. Similar results were observed for plasma NDI-011535. Mean plasma NDI-011535 exposure was < 10% of GS-0976 plasma exposure, based on metabolite-to-parent (MPR) C_{max} and MPR AUC_{inf}.

Table 1-1. Summary of Single Dose Pharmacokinetic Parameters of GS-0976 Following Administration of 30 mg to 1000 mg GS-0976 Under Fasting Conditions and 200 mg GS-0976 Under Fed Conditions

PK Parameter Mean ± SD	GS-0976 Dose (mg)						
	30 mg Fasted (N=6)[a]	80 mg Fasted (N=6)[a]	200 mg Fasted (N=6)[a]	200 mg Fed (N=6)[a]	500 mg Fasted (N=6)[b]	800 mg Fasted (N=6)[b]	1000 mg Fasted (N=6)
Plasma							
AUC_{0-t} (ng*h/mL)	176 ± 104	363 ± 215	1210 ± 537	1160 ± 613	2930 ± 2440	6420 ± 3180	17,400 ± 8400
AUC_{0-inf} (ng*h/mL)	179 ± 115	402 ± 225	1250 ± 616	1260 ± 683	2960 ± 2460	6460 ± 3190	17,500 ± 8410
C_{max} (ng/mL)	79.7 ± 65.9	101 ± 47.8	416 ± 211	134 ± 70.1	1110 ± 1150	2570 ± 1880	8380 ± 3210
T_{max} (h)[c]	1.26 (0.23, 2.00)	2.00 (1.50, 2.00)	1.50 (1.01, 4.00)	2.00 (1.50, 24.0)	1.75 (1.01, 3.00)	2.01 (1.01, 3.00)	2.50 (1.02, 4.01)
$T_{1/2}$ (h)	4.47 ± 1.56	6.98 ± 2.81	11.7 ± 1.35	8.70 ± 2.10	10.2 ± 2.13	8.24 ± 3.26	9.46 ± 2.60
CL/F (L/h)	250 ± 178	251 ± 124	189 ± 76.5	212 ± 131	290 ± 188	146 ± 57.4	65.2 ± 21.3
V_z/F (L)	1730 ± 1510	2360 ± 1390	3150 ± 1270	2500 ± 1290	4190 ± 2570	1620 ± 561	904 ± 469
Urine							
A_{e0-48} (µg)	9.72 ± 8.73	25.8 ± 11.7	48.8 ± 21.3	N/C	135 ± 106	1030 ± 924	636 ± 600
F_e (%)	0.032 ± 0.029	0.032 ± 0.015	0.024 ± 0.011	N/C	0.027 ± 0.021	0.129 ± 0.115	0.064 ± 0.060
CL_{Renal} (mL/h)	50.0 ± 45.1	109 ± 96.2	46.2 ± 15.5	N/C	77.5 ± 65.7	135 ± 62.2	42.6 ± 36.5

PK parameters are presented to 3 significant digits, N/C = Not Calculated
a N=5 for AUC_{0-inf}, $T_{1/2}$, CL/F, and V_z/F
b N=5 for A_{e0-48}, F_e, and CL_{renal}
c T_{max} is presented as median (minimum, maximum)
The A_{e0-48}, F_e, and Cl_{renal} for subject PPD (500 mg GS-0976) were missing, because this subject was unable to provide urine samples during the 12-24 hour, 24-36 hour, and 36-48 hour intervals, due to an AE.
The A_{e0-48}, F_e, CL_{renal} for subject PPD (800 mg GS-0976) were excluded from the summary statistics, because the urine sample for the 24-36 hour collection interval was partially spilled prior to volume measurement (ie, calculations were based off an approximate urine volume)

1.2.5.2. Study 0976-102: Multiple Ascending Dose (MAD) Study

The multiple ascending dose (MAD) study (Protocol Number 0976-102) was a randomized, double-blind, placebo-controlled, clinical study conducted in healthy adult subjects at one study center in the United States. Five (5) cohorts of 8 subjects (6 active and 2 placebo) were evaluated at the following GS-0976 doses: 50 mg BID (100 mg daily) or placebo, 100 mg QD (100 mg daily) or placebo, 100 mg BID (200 mg daily) or placebo, 200 mg QD (200 mg daily) or placebo, or 150 mg QD (150 mg daily) or placebo. In each cohort, subjects received multiple

oral doses of GS-0976 or placebo BID (every 12 hours) or once daily (QD) for 9 consecutive days (Days 1 through 9), with a single oral dose of GS-0976 or placebo on the morning of Day 10. Doses were administered approximately 30 minutes after meals. Preliminary safety and PK data are available for the first 4 dose groups.

Each of the first 4 dose groups was fully enrolled and, overall, 24 subjects received GS-0976 and 8 subjects received placebo. The majority of these 32 subjects who received GS-0976 (19/24, 79%) and placebo (4/8, 50%) had at least 1 treatment-related AE as assessed by the principal investigator. The incidence of treatment-related AEs appeared to increase with higher doses and BID dosing of GS-0976: 50% of subjects at 50 mg BID, 62.5% at 100 mg QD, 75% at 200 mg QD, and 100% at 100 mg BID. One subject in the 200 mg QD cohort discontinued due to an AE on study Day 7 for Grade 4 elevated triglycerides (TG). No deaths or SAEs were reported.

The most frequently reported TEAEs were gastrointestinal disorders and involved nausea (33% of all subjects who received GS-0976 vs. 0% of all subjects who received placebo), abdominal distension (25% GS-0976 vs. 13% placebo), constipation (21% GS-0976 vs. 13% placebo), diarrhea (21% GS-0976 vs. 0% placebo), and vomiting (13% GS-0976 vs. 0% placebo). In addition, TEAEs of increased blood triglycerides were reported (25% GS-0976 vs. 0% placebo) and involved Grade 3 events in 5 subjects (3 subjects in the 100 mg BID cohort and 2 subjects in the 50 mg BID cohort), and a Grade 4 event in 1 subject in the 200 mg QD cohort (discontinued treatment).

There were no clinically important treatment-related or dose-related trends in vital signs, ECG, or physical examination assessments in this study.

Preliminary single (Day 1) and (Day 10) multiple dose PK parameters for GS-0976 and ND-011535 after administration of 50 mg BID, 100 mg QD, 100 mg QD, and 200 mg QD GS-0976 under fed conditions are presented Tables 1-2 and 1-3, respectively. In general, GS-0976 AUC and C_{max} increased in a dose proportional manner across the doses evaluated. GS-0976 AUC accumulated approximately 2-fold on Day 10 compared to Day 1 with minimal accumulation of C_{max}. Median GS-0976 T_{max} occurred between 3 and 6 hours, in agreement with the food effect observed in study 0976-101. The mean $T_{1/2}$ of GS-0976 ranged from 3.5-10.3 hours with higher variability contributing to the higher mean estimates from Day 10 in the 50 mg BID and 100 mg QD cohorts. Mean plasma NDI-011535 exposure was < 10% of GS-0976 plasma exposure, based on MPR for AUC and C_{max}. The PK profile of NDI-011535 was consistent with the PK profile of GS-0976, as seen by the consistent MPR for AUC_{inf} and C_{max} on Day 1 and Day 10 as well as across the doses evaluated. NDI-011535 exhibits formation rate limited kinetics as the mean $T_{1/2}$ of NDI-011535 was consistent with that observed for GS-0976.

Table 1-2. Summary of Single and Multiple Dose Pharmacokinetic Parameters of GS-0976 Following Administration of 50 mg BID, 100 mg QD, 100 mg BID, or 200 mg QD GS-0976 Under Fed Conditions

Plasma PK Parameter Mean ± SD	GS-0976 Dose			
	50 mg BID Fed (N=6)	100 mg QD Fed (N=6)	100 mg BID Fed (N=6)	200 mg QD Fed (N=6)
Day 1				
$AUC_{0\text{-}12or24}$ (ng*h/mL)	143 ± 29.1	268 ± 95.7	345 ± 77.0	868 ± 221
$AUC_{0\text{-}inf}$ (ng*h/mL)	178 ± 40.7[a]	278 ± 110[a]	671[b]	979 ± 286[a]
C_{max} (ng/mL)	41.3 ± 14.3	64.9 ± 31.7	61.6 ± 14.7	152 ± 68.4
T_{max} (h)[c]	2.50 (1.50, 3.02)	3.50 (1.00, 6.00)	5.02 (3.00, 8.00)	5.00 (2.00, 6.00)
$T_{1/2}$ (h)	3.50 ± 1.63[a]	4.33 ± 0.741[a]	5.58[b]	5.86 ± 3.59[a]
CL/F (L/h)	292 ± 61.6[a]	403 ± 139[a]	149[b]	219 ± 64.0[a]
V_z/F (L)	1350 ± 333[a]	2560 ± 1180[a]	1120[b]	1710 ± 720[a]
Day 10				
$AUC_{0\text{-}tau}$ (ng*h/mL)	305 ± 77.0	369 ± 160	742 ± 217	1770 ± 573[a]
RAUC	2.13 ± 0.279	1.37 ± 0.323	2.23 ± 0.766	2.10 ± 0.636[a]
C_{max} (ng/mL)	49.4 ± 15.2	53.5 ± 22.4	121 ± 56.3	198 ± 86.6[a]
C_{ave} (ng/mL)	25.4 ± 6.42	15.4 ± 6.68	61.8 ± 18.1	73.7 ± 23.9[a]
C_{trough} (ng/mL)	12.4 ± 5.04	3.16 ± 2.24	56.1 ± 22.7	33.9 ± 42.9[a]
T_{max} (h)[c]	4.01 (2.05, 8.00)	3.01 (2.00, 12.0)	6.00 (2.00, 6.00)	4.00 (1.50, 6.00)[a]
$T_{1/2}$ (h)	10.3 ± 6.66	7.92 ± 4.52	6.83 ± 1.62	5.91 ± 0.987[a]
CL_{ss}/F (L/h)	173 ± 41.5	312 ± 116	145 ± 43.5	125 ± 46.4[a]

PK parameters are presented to 3 significant digits
RAUC = Ratio of Day 10 $AUC_{0\text{-}tau}$ / Day 1 $AUC_{0\text{-}t}$
a N=5
b N=1
c T_{max} is presented as median (minimum, maximum)

Table 1-3. Summary of Single and Multiple Dose Pharmacokinetic Parameters of ND-011535 Following Administration of 50 mg BID, 100 mg QD, 100 mg BID, or 200 mg QD GS-0976 Under Fed Conditions

Plasma PK Parameter Mean ± SD	GS-0976 Dose			
	50 mg BID Fed (N=6)	100 mg QD Fed (N=6)	100 mg BID Fed (N=6)	200 mg QD Fed (N=6)
Day 1				
$AUC_{0\text{-}12or24}$ (ng*h/mL)	11.6 ± 3.57[a]	23.7 ± 0.891[b]	29.9 ± 15.1[a]	78.8 ± 43.3[c]
MPR AUC	0.064 ± 0.022[c]	0.042[d]	0.063 ± 0.027[a]	0.0636 ± 0.027[c]
C_{max} (ng/mL)	3.14 ± 1.39	3.98 ± 2.29	4.36 ± 2.63	9.54 ± 6.66
MPR C_{max}	0.057 ± 0.013	0.051 ± 0.023	0.054 ± 0.028	0.048 ± 0.020
T_{max} (h)[e]	2.50 (1.50, 302)	3.50 (1.50, 6.00)	6.00 (4.00, 11.9)	6.00 (4.00, 6.00)
$T_{1/2}$ (h)	5.13 ± 2.93[a]	3.59 ± 0.895[b]	N/C	7.55 ± 2.06[c]
Day 10				
$AUC_{0\text{-}tau}$ (ng*h/mL)	28.5 ± 8.89	46.0 ± 22.6[f]	67.0 ± 31.6	129 ± 74.3[a]
RAUC	2.49 ± 0.32[a]	2.50 ± 0.150[b]	1.93 ± 0.752[a]	2.41 ± 1.03[f]
MPR AUC	0.072 ± 0.013	0.073 ± 0.015 N=3	0.050 ± 0.020	0.052 ± 0.016[a]
C_{max} (ng/mL)	4.92 ± 1.90	4.52 ± 3.82	6.62 ± 2.84	12.2 ± 5.33[a]
C_{ave} (ng/mL)	2.37 ± 0.741	1.92 ± 0.943[f]	3.95 ± 1.64	5.38 ± 3.09[a]
MPR C_{max}	0.075 ± 0.014	0.057 ± 0.028	0.046 ± 0.019	0.051 ± 0.02[a]
C_{trough} (ng/mL)	1.20 ± 0.383	0.575 ± 0.078[b]	3.76 ± 1.45	3.21 ± 3.18[c]
T_{max} (h)[e]	3.50 (2.05, 6.00)	4.51 (2.00, 6.02)	6.00 (1.50, 6.04)	6.00 (3.00, 6.00)[a]
$T_{1/2}$ (h)	4.61 ± 1.30[a]	6.00 ± 0.225[b]	5.67 ± 0.40[b]	5.14 ± 2.14[f]

PK parameters are presented to 3 significant digits
RAUC = Ratio of Day 10 $AUC_{0\text{-}tau}$ / Day 1 $AUC_{0\text{-}t}$
MPR = Metabolite to Parent Ratio corrected for molecular weight
N/C = Not Calculated
a N=5
b N=2
c N=4
d N=1
e T_{max} and $T_{1/2}$ are presented as median (minimum, maximum)
f N=3

1.2.5.3. Study 0976-103: Single Ascending Dose Pharmacodynamic Study

The single ascending dose PD study (Study 0976-103) was a two-period, two-treatment, crossover, randomized, double-blind, study to determine the PD activity on fractional DNL of a single oral dose of 20, 50, or 200 mg of GS-0976 compared to placebo in 3 cohorts of 10 adult male subjects who were overweight and/or obese, but otherwise healthy, at each dose level (total 30 subjects). Subjects were randomized in Period 1 to receive a single oral dose of either

GS-0976 or matched placebo followed by a washout and administration of the opposite study medication in Period 2.

The objectives of the study were to assess the following after a single oral dose of GS-0976 in overweight and/or obese, but otherwise healthy, adult male subjects: PD effects of GS-0976 on fractional DNL, safety and tolerability of GS-0976, correlation of PK and PD effects, and PK parameters.

Fractional DNL was evaluated by utilizing a qualified method that measured the appearance of de novo synthesis of palmitate in very-low density lipoproteins (VLDL) in response to oral fructose using [^{13}C] acetate incorporation into palmitate and mass isotopomer distribution analysis (MIDA). Review of the data demonstrated mean inhibition of fractional DNL (71%, 87%, and 98% by AUC) by GS-0976 at 20, 50, and 200 mg, respectively, compared to matched placebo.

A total of 41 TEAEs were experienced by 15 (52%) subjects following administration of GS-0976 (28 considered possibly related); 22 TEAEs were experienced by 12 (40%) pooled placebo subjects (17 considered possibly related), and 4 TEAEs were experienced by 4 (13%) subjects following the [^{13}C] acetate infusion. Gastrointestinal events including diarrhea (11/29, 38% GS-0976 vs. 9/30, 30% placebo) and flatulence (5/29, 17% GS-0976 vs. 3/30, 10% placebo) were the most common TEAEs following both active and placebo treatments. The incidence of treatment emergent AEs did not increase with rising GS-0976 dose levels. Most TEAEs in the study were of Grade 1 severity (39/41, 95 %) and were resolved by study completion. Three subjects experienced 4 TEAEs of Grade 2 severity including headache and nausea (placebo), arthralgia (GS-0976 20 mg), and dyspepsia (GS-0976 20 mg). No deaths or SAEs were reported.

Overall, no clinically important trends in changes over time were noted in the laboratory results for GS-0976 active groups compared to placebo.

1.3. Rationale for the Current Study

Current evidence suggests that NASH is a consequence of the metabolic syndrome and lipotoxicity in the steatotic liver, which sets off an inflammatory response with subsequent activation of hepatic stellate cells and fibrogenesis. A key finding in patients with NASH is upregulation of the hepatic synthesis of fatty acids and triglycerides, referred to as de novo lipogenesis (DNL). Enhanced DNL in NASH occurs despite the excessive delivery of fatty acids to the liver from the diet as chylomicrons and from adipose tissue via lipolysis {Lambert 2014}. DNL-derived fatty acids and their byproducts (e.g. diacylglycerol, lysophosphatidic acid, and eicosanoids) represent important signaling mediators that drive the lipotoxicity and inflammation characteristic of NASH {Neuschwander-Tetri 2010}. The first and rate-limiting step in DNL is the conversion of acetyl-coA to malonyl-coA by acetyl-coA carboxylase (ACC). ACC exists as two isoforms (ACC1 and ACC2). Whereas ACC1 is a cytosolic enzyme present in lipogenic tissues (e.g. liver and adipose), ACC2 is a mitochondria-associated enzyme present in oxidative tissues (e.g. liver, heart, and skeletal muscle) {Bianchi 1990, Kim 1997}. Inhibition of ACC1 reduces DNL in lipogenic tissues while inhibition of ACC2 in oxidative tissues enhances

mitochondrial fatty acid oxidation {Harwood 2005}. Due to this unique position in intermediary metabolism {Harwood 2005, Tong 2006}, pharmacologic inhibition of ACC is an attractive strategy for limiting fatty acid synthesis while simultaneously stimulating fatty acid oxidation.

GS-0976 is a highly potent and selective allosteric inhibitor of ACC1 and ACC2. Pharmacodynamic studies indicate that GS-0976 reduces DNL, hepatic steatosis, inflammatory mediators, and fibrosis in preclinical models of liver disease {Harriman 2016}. In addition, GS-0976 improves metabolic parameters (e.g. plasma triglycerides and free fatty acids, insulin, and leptin sensitivity) in high fat and high sucrose diet-induced obesity models. In total, these studies confirm the potential for GS-0976 to impact important histologic endpoints in NASH and also ameliorate the metabolic dysfunction frequently observed in these patients. Moreover, the liver-directed biodistribution of GS-0976 ensures that pharmacological effects are focused on the key target tissue for NASH and is anticipated to minimize effects outside of the liver.

In summary, the totality of the preclinical and clinical evidence, in addition to the large unmet medical need and the lack of existing therapies, suggests that the evaluation of GS-0976 in subjects with NASH, as proposed in the current study, is of merit.

1.3.1. Rationale for this Study

This Phase 2 study has been designed as a multicenter, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of GS-0976 for 12 weeks in subjects with NASH. Approximately 125 NASH subjects without cirrhosis will be randomized in a 2:2:1 ratio to receive GS-0976 at a dose of 5 mg or 20 mg orally QD, or placebo. Randomization will be stratified by the presence or absence of diabetes mellitus, a common comorbidity in patients with this condition.

Inclusion criteria for the study were developed in order to noninvasively identify subjects with NASH. Specifically, all subjects will have a clinical diagnosis of NAFLD and evidence of NASH histologically or based on magnetic resonance imaging; specifically, ≥ 8% hepatic steatosis on MRI-PDFF {Bannas 2015} and increased liver stiffness on MRE (≥ 2.5 kPa) {Park 2016}. Previous studies have shown that patients with NAFLD and increased liver stiffness by MRE have a high probability of NASH on liver biopsy. For example, Park et al. reported that an MRE liver stiffness cut-off of ≥ 2.53 kPa was 64% sensitive, 68% specific, and had an area under the receiver operating characteristic curve (AUROC) of 0.70 and positive predictive value of 87% for the differentiation of simple steatosis from NASH on biopsy. Moreover, in this cohort of 104 patients, Park et al. demonstrated that a liver stiffness by MRE ≥ 2.65 kPa optimally identified the presence of at least stage 1 fibrosis (AUROC 0.82). Based on these criteria, subjects enrolled in this study have a high probability of NASH with fibrosis, a population with a large unmet medical need {Loomba 2014}. Since the safety and PK of GS-0976 have not yet been explored in subjects with cirrhosis, criteria have been developed in order to exclude cirrhotic subjects based on a validated serum marker for fibrosis (FibroTest®) and historical clinical, histological, and imaging data {Ratziu 2006}.

The primary endpoint of this study will be the safety and tolerability of GS-0976. In addition, the biological activity of GS-0976 will be determined based on endpoints including routine liver

biochemistry (e.g. ALT and GGT); noninvasive serum markers of liver injury (e.g. serum CK-18, FibroTest® and ELF™ Test); and imaging-based methods for quantifying hepatic steatosis (MRI-PDFF) and fibrosis (MRE and FibroScan®). An important endpoint of interest is the proportion of subjects achieving ≥ 30% reduction in steatosis as assessed by MRI-PDFF. This level of reduction has been associated with a significant improvement in NASH histology (≥ 2-point reduction in NAFLD Activity Score) {Patel 2015}. Based on preclinical and clinical data, a treatment duration of 12 weeks with GS-0976 is expected to be sufficient to lead to meaningful improvements in hepatic steatosis on MRI-PDFF and liver biochemistry. Liver histology has not been included as an endpoint because it is not feasible to repeat this invasive procedure over a 12-week study. In addition to these liver-related endpoints, the effects of GS-0976 on carbohydrate and lipid metabolism (e.g. with glucose, insulin, free fatty acids, apolipoproteins, lipid profiles, and metabolites) will be closely monitored in light of the mechanism of action of GS-0976 and the importance of metabolic dysfunction in contributing to the morbidity and mortality (e.g. cardiovascular) of subjects with NASH.

The doses of GS-0976 chosen for evaluation in this study, 5 and 20 mg QD for 12 weeks, are supported by the safety, tolerability and effects of GS-0976 on DNL from studies 0976-101, 0976-102, and 0976-103. As described in Section 1.2.5, single doses of GS-0976 up to 1000 mg or multiple daily doses (10 days) up to 200 mg were administered safely to healthy subjects in these studies. Moreover, a single dose of 20 mg resulted in a mean inhibition of fractional DNL of 71%. This level of DNL is postulated to be sufficient to achieve meaningful reductions in hepatic steatosis and lipid-derived inflammatory mediators that contribute to the pathogenesis of NASH. The four-fold GS-0976 dose range in this study will assess the impact of a range of GS-0976 systemic exposure on safety and effect of GS-0976 in subjects with NASH. Additionally, nonclinical toxicology studies up to 13 weeks in duration have been conducted in rats and dogs at exposure margins multiple folds above the expected clinical exposure. Based on preliminary data from studies 0976-101 (Section 1.2.5.1) and 0976-102 (Section 1.2.5.2), GS-0976 exposures in this study are expected to remain > 15 to 23-fold lower than the GS-0976 exposures observed at the NOAELs in the 13-week rat and dog studies, respectively.

1.4. Risk/Benefit Assessment for the Study

This study will provide information on the safety and efficacy of GS-0976 for the treatment of patients with NASH. As there are currently no approved therapies for NASH, there is a large unmet medical need for this growing population of patients.

The potential benefits of GS-0976 for the treatment of NASH in the current study population include hypothesized improvements in hepatic steatosis and inflammation due to reduced DNL and increased beta oxidation that have been observed in pre-clinical and/or clinical studies of ACC inhibition. Improvements in liver biochemistry and hepatic fibrogenesis would be expected to ensue based on these effects.

To date, 96 subjects have received GS-0976 in Phase 1 studies in single doses up to 1000 mg or multiple daily doses (10 days) up to 200 mg. In general, treatment emergent adverse events (TEAEs) were mild to moderate with the predominant toxicities being gastrointestinal

(e.g. nausea, flatulence, diarrhea, constipation) in nature (see Section 1.2.5). Asymptomatic, Grade 3 or 4 elevations in blood triglycerides have been noted in 6 subjects treated for 10 days with GS-0976 at daily doses of 100 mg or higher. There is a potential risk to study participants of experiencing these and previously undetected side effects with longer term GS-0976 dosing. However, lower doses of 5 mg and 20 mg daily have been chosen for this study in order to mitigate this potential risk. 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 laboratory abnormalities will be well-defined and closely followed.

In summary, there are no approved treatment options available for patients with NASH. Based on past clinical experience with GS-0976, the risk/benefit is positive and supports the continued evaluation of GS-0976 in this patient population. Data from this study will support the development of GS-0976 for the treatment of this condition.

1.5. Compliance

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

2. OBJECTIVES

The **primary objective** of this study is as follows:

- To evaluate the safety and tolerability of GS-0976 in subjects with NASH.

The **exploratory objectives** of this study are as follows:

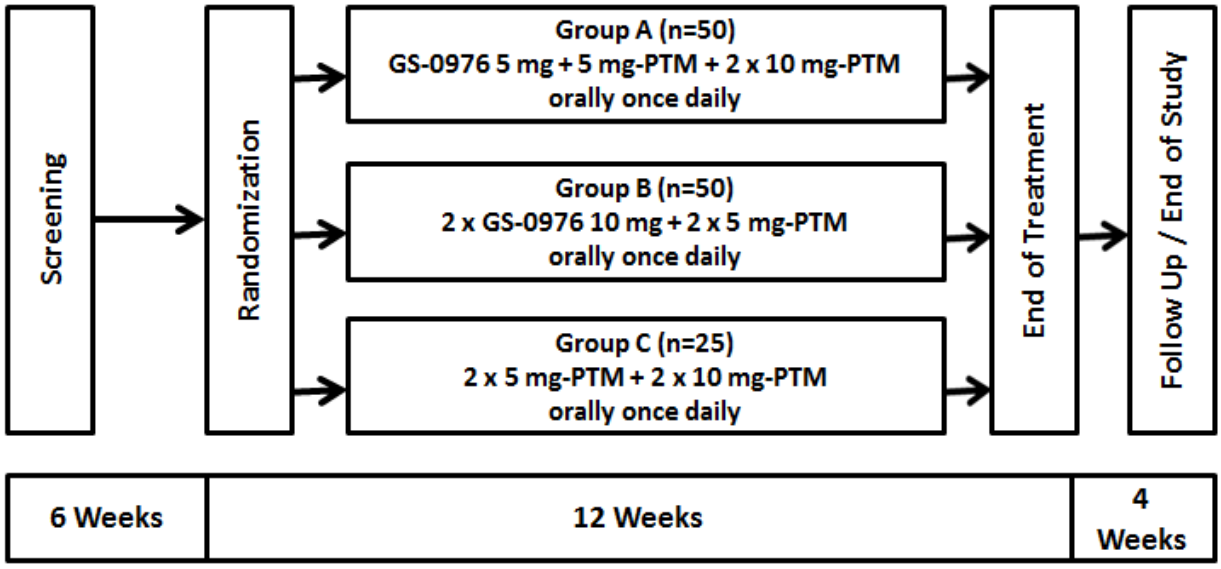
3. STUDY DESIGN

3.1. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and efficacy of GS-0976 in subjects with NASH. To be eligible to participate, subjects must have evidence of hepatic steatosis and increased liver stiffness as assessed by MRI-PDFF and MRE, respectively, or a historical liver biopsy consistent with NASH and non-cirrhotic fibrosis. Any subject with history of decompensated liver disease, including ascites, hepatic encephalopathy or variceal bleeding will be ineligible.

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 different treatment groups, A, B, and C, as shown in Figure 3-1. Randomization will be stratified by the presence or absence of diabetes mellitus as determined by medical history, use of medication for indication of diabetes mellitus, or based on Screening lab values if previously undiagnosed (i.e., hemoglobin A1c ≥ 6.5% OR fasting plasma glucose ≥ 126 mg/dL).

Study drugs will be administered for a total of 12 weeks from the Baseline/Day 1 visit. Dosage and administration of the study drugs and reference product are described in Section 5.3.

3.3. Biomarker Testing

3.3.1. Biomarker Samples to Address the Study Objectives

Biological specimens will be collected in this study as per the study procedures table to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drugs response, pathway markers, including efficacy and/or adverse events and to increase knowledge and understanding of the biology of NASH or related diseases such as liver fibrosis, and inflammatory diseases and/or the validation of a companion diagnostic for GS-0976 based upon the current state of scientific knowledge. Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that will be done on the specimens provided. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge. Samples will be will be stored for up to 15 years after the end of study.

3.3.2. Biomarker Samples for Optional Future Research

CCI [redacted]

3.3.3. Biomarker Samples for Optional Genomic Research

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will enroll approximately 125 subjects with NASH.

4.2. Inclusion Criteria

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

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

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

3) Meets the following conditions:

   a) A clinical diagnosis of NAFLD with imaging or a liver biopsy documenting fatty liver within two years prior to Screening (if necessary, an ultrasound may be performed during Screening to confirm NAFLD), and

   b) Screening MRI-PDFF with ≥ 8% steatosis, and

   c) Screening MRE with liver stiffness ≥ 2.5 kPa.

      Note: criterion 3a. must be met before evaluating criteria 3b. and 3c.

      OR

   d) A historical liver biopsy within 12 months of Screening consistent with NASH (defined as the presence of steatosis, lobular inflammation, and hepatocellular ballooning) with fibrosis, but not cirrhosis, and

   e) No documented weight loss > 5% between the date of the liver biopsy and Screening.

4) Platelet count ≥ 100,000/mm3

5) Creatinine Clearance (CLcr) as calculated by the Cockcroft-Gault equation ≥ 60 ml/min

6) Female subjects of childbearing potential (see definition in Appendix 3) must have a negative serum pregnancy test prior to starting study treatment;

7) All female subjects of childbearing potential who engage in heterosexual intercourse must agree to use a highly effective method of contraception during intercourse from the Screening visit throughout the study period and for 30 days following the last dose of study drugs (see Appendix 3 for details);

8) Male subjects are required to use barrier contraception (condom plus spermicide) during intercourse from the Screening through the study completion and for 90 days following the last dose of study drugs (see Appendix 3 for details);

9) Male subjects must refrain from sperm donation from Screening through at least 90 days following the last dose of study drugs.

10) Female subjects must refrain from egg donation or harvest for 30 days after last dose of study drugs.

11) Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

12) Must be able to read and complete Quality of Life questionnaires independently.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria will not be randomized in this study.

1) Pregnant or lactating females; lactating females must agree to discontinue nursing before the study drugs are administered;
2) ALT > 5 x ULN;
3) Other causes of liver disease including autoimmune, viral, and alcoholic liver disease;
4) Cirrhosis of the liver as defined by any of the following:
   a) Cirrhosis on historical liver biopsy (e.g. NASH CRN classification stage 4 or equivalent);
   b) Evidence of cirrhosis on liver imaging (e.g. ultrasound, CT, or MRI) including a nodular liver surface, splenomegaly, or portal venous collaterals;
   c) Prior history of decompensated liver disease, including ascites, hepatic encephalopathy or variceal bleeding;
   d) Screening FibroSURE/FibroTest® ≥ 0.75, unless a historical liver biopsy within 12 months of Screening does not reveal cirrhosis. In patients with Gilbert's syndrome or hemolysis, FibroSURE/FibroTest® will be calculated using direct bilirubin instead of total bilirubin.
5) History of liver transplantation;
6) Weight reduction surgery in the 2 years prior to Screening or planned during the study (weight reduction surgery is disallowed during the study);
7) History of intestinal resection or malabsorptive condition that may limit the absorption of GS-0976. Prior cholecystectomy and appendectomy are permitted

8) BMI < 18 kg/m^2;

9) INR > 1.2, unless on anticoagulant therapy;

10) Total bilirubin > 1 x ULN, except with diagnosis of Gilbert's syndrome;

11) Chronic hepatitis B (HBsAg positive);

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

13) HIV Ab positive;

14) 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);

15) Positive urine 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;

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

    a) Unstable angina within 6 months prior to Screening

    b) Myocardial infarction, coronary artery bypass graft surgery or coronary angioplasty within 6 months prior to Screening

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

    d) Obstructive valvular heart disease or hypertrophic cardiomyopathy

    e) Congestive heart failure;

17) Use of prohibited concomitant medications as described in Section 5.4

18) History of a malignancy within 5 years prior to 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;

19) 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;

20) Participation in another investigational study of a drug or device within 28 days prior or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Screening;

21) Concurrent participation in another therapeutic clinical study;

22) Known hypersensitivity to GS-0976, the metabolites, or formulation excipient;

23) Presence of any condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, such as history of substance abuse or a psychiatric (including any subjects with a psychiatric hospital admission or emergency room visit in the 2 years prior to Screening) or medical condition;

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

25) Contraindications or inability to complete MRI scanning (e.g. presence of permanent pacemakers, implanted cardiac devices, weight restrictions, etc.).

Subjects with laboratory abnormalities outside of the above parameters may be approved for inclusion in the trial with approval from the Medical Monitor.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

This is a randomized, double-blind, placebo-controlled study. Subjects meeting the study entry criteria will be randomly assigned in a 2:2:1 ratio to 1 of 3 different treatment group 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, use of medication for indication of diabetes mellitus, or based on Screening lab values if previously undiagnosed (ie, hemoglobin A1c ≥ 6.5% OR fasting plasma glucose ≥ 126 mg/dL).

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 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 (or designee) 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 Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Study Drugs

5.2.1. Formulation

GS-0976 will be supplied as white opaque size 0 hard gelatin capsules containing 10 mg of GS-0976, and as white opaque size 2 hard gelatin capsules containing 5 mg of GS-0976. In addition to the active ingredient, GS-0976 capsules contain the following inactive ingredients: lactose monohydrate, stearoyl polyoxylglycerides and croscarmellose sodium, which are common pharmaceutical excipients.

Placebo-to-match (10 mg-PTM and 5 mg-PTM) GS-0976 capsules are identical in size, shape, color and appearance to their corresponding strengths of active GS-0976 capsules. PTM GS-0976 capsules contain lactose monohydrate.

5.2.2. Packaging and Labeling

GS-0976 capsules and PTM GS-0976 are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 capsules. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

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

5.2.3. Storage and Handling

GS-0976 and PTM GS-0976 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.

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 GS-0976/PTM GS-0976

GS-0976 capsules will be provided by Gilead Sciences. Subjects will take 4 capsules of GS-0976 (5 mg, 5 mg-PTM, 10 mg, or 10 mg-PTM) once daily at approximately the same time each morning. Study drugs 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: GS-0976 5 mg (1 x 5 mg capsule + 1 x 5 mg-PTM capsule + 2 x 10 mg-PTM capsules) administered orally once daily;
- Treatment Group B: GS-0976 20 mg (2 x 10 mg capsules + 2 x 5 mg-PTM capsules) administered orally once daily;
- Treatment Group C: GS-0976 Placebo (2 x 5 mg-PTM capsules + 2 x 10 mg-PTM capsules) 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 from 28 days prior to Baseline/Day 1 up to and including the day of the last dose of study drugs:

- Hematologic stimulating agents (e.g. erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)
- Chronic systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (eg, infliximab). Use for ≤ 2 weeks total is allowed.
- Investigational agents or devices for any indication
- Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters P-gp, or OATP1B3 or 1B3, or substrates of CYP3A which are sensitive to induction) with GS-0976 may result in PK interactions resulting in increases or decreases in exposure of GS-0976 or concomitant medications. Examples of representative medications which are prohibited from 28 days prior to Baseline/Day 1 through the treatment period are listed below in Table 5-1:

Table 5-1. List of Prohibited Medications

Drug Class	Agents Disallowed
Antibiotics	Azithromycin, Clarithromycin, Erythromycin
Anticonvulsants[a]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antifungals	Itraconazole, Ketoconazole
Antimycobacterials[a]	Rifamycins, Isoniazid
Cardiac Medications	Amiodarone, Digoxin, Dronedarone, Felodipine, Verapamil, Quinidine, Ranolazine, Bosentan, Olmesartan, Telmisartan, Valsartan
Herbal/Natural Supplements[a]	St. John's Wort, Echinaccea. Milk thistle (i.e. silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Selective Serotonin Reuptake Inhibitors	Fluvoxamine
Other	Gemfibrozil, Modafinil

a May result in a decrease in the concentrations of study drugs.

Medications for disease conditions **excluded** from the protocol (e.g., HIV-1, HBV, or HCV infection, active cancer, transplantation) are not listed under this Concomitant Medication section and are disallowed in the study.

5.5. Accountability for GS-0976/PTM GS-0976

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. All used and unused study drug bottles dispensed to subjects must be returned to the site.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug bottles
- Record the date, subject number, subject initials, and the study drug bottle number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

Refer to Section 9.1.7 for instructions regarding study drug return or disposal.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject randomized 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 Reference Binder.

The investigator must document any deviation from protocol procedures and notify the Sponsor or the 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 6 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.

Subjects who previously failed screening in GS-US-426-3989 can be re-screened in the following situations:

- Previously screen failed due to a low MRE or MRI-PDFF measurement, but have an MRE ≥ 2.5 kPa and MRI-PDFF ≥ 8% within 6 months of prior Screening/Re-screening.
- Previously screen failed due to a low MRE or MRI-PDFF measurement and have a historical liver biopsy within 12 months of Screening/Re-screening that is consistent with NASH (defined as the presence of steatosis, hepatocellular ballooning, and lobular inflammation) with fibrosis, but not cirrhosis.
- Previously screen failed due to a FibroSURE/FibroTest® ≥ 0.75 in whom Gilbert's syndrome or hemolysis is present; a repeat FibroSURE/FibroTest® calculated using direct bilirubin instead of total bilirubin will be used to determine eligibility.

- Previously screen failed due to a FibroSURE/FibroTest® ≥ 0.75 and with a historical liver biopsy within 12 months of Screening that does not reveal cirrhosis; FibroSure/Fibrotest score will not be used to determine eligibility.

If MRE and MRI-PDFF were performed within 6 months of re-screening, MRE and MRI-PDFF does not need to be repeated. If prior imaging was performed greater than 6 months prior to re-screening, MRE and MRI-PDFF must be repeated. A historical MRE and MRI-PDFF within 6 months of screening in another Gilead study (i.e. GS-US-384-3914, GS-US-402-1852) may be used to determine eligibility into this study. All other screening procedures must be repeated and meet eligibility criteria.

Screening labs may be repeated within the Screening period, prior to administration of study drugs to rule out laboratory error, if any. This will be done at the discretion of the investigator.

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 fasted 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 physical examination
- Record vital signs, body weight, and height
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Hemoglobin A1c
  - HIV-1, HBV and HCV serology (if HCV Ab positive, reflex to HCV RNA.)
  - Serum pregnancy test (only for female subjects of child bearing potential - see Appendix 3.)

— CCI [redacted]

- Conduct standard 12-Lead ECG
- Perform ultrasound (if necessary) for confirmation of NAFLD
- Perform MRE and MRI-PDFF
- Review any historical liver biopsy results, if available.
- Urine drug screen for amphetamines, cocaine and opiates (i.e., heroin, morphine)
- Record all concomitant medications that the subject has taken within 30 days prior to Screening
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 6 weeks of the start of Screening for randomization into the study. The screening period may be extended under special circumstances with the explicit approval of the Medical Monitor.

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 electronic case report form (eCRF). All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Baseline/Day 1 Randomization and Assessments

Subjects returning to the clinic for randomization at Baseline/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 Baseline/Day 1 visit to ensure an approximate 8-hour fast prior to the blood sample collection under fasting conditions 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, use of medication for indication of diabetes mellitus, or based on Screening lab values if previously undiagnosed (ie, hemoglobin A1c $\geq$ 6.5% OR fasting plasma glucose $\geq$ 126 mg/dL).

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

- QoL Questionnaires (SF-36, WPAI, and CLDQ)

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

- Symptom driven physical examination
- Record vital signs, waist circumference, and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
  - Hemoglobin A1c
  - Biomarkers
  - CCI [redacted]
- Conduct standard 12-Lead ECG
- Perform FibroScan® (if available)
- Collect urine samples for:
  - Urine pregnancy test for females of child bearing potential only
  - Biomarkers
- Collect stool sample for Biomarkers (see Study Reference Binder for instructions)
- Dispense study drugs, and provide subject with instruction on appropriate dosing and administration; subject will take the Baseline/Day 1 dose of study drugs on-site
- 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 Screening visit

Subjects will return to the investigative site at Week 1 (±3 days) for a mandatory safety visit. Then, starting at the Week 4 visit, subjects will have visits every 4 weeks up to the Week 12 visit.

6.4. Treatment Assessments

6.4.1. Week 1 Visit (±3 days)

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

Subjects should also be instructed to HOLD their dose of study drugs on the day of their Week 1 visit until all visit procedures have been completed. The study drugs should be taken after the visit.

During the Week 1 safety visit (±3 days), the subject will return to the investigative site and the following will be performed and documented:

- Symptom driven physical examination
- Record vital signs, and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
  - Biomarkers
  - Single PK sampling
- Collect urine sample for biomarkers
- 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 Visit (±3 days)

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the Week 4 visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Subjects should also be instructed to HOLD their dose of study drugs on the day of their Week 4 visit until all visit procedures have been completed. The study drugs should be taken after the visit.

The following will be performed and documented at this visit (±3 days):

- Symptom driven physical examination
- Record vital signs, and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
  - Biomarkers
  - Single PK sampling
- Collect urine samples for:
  - Urine pregnancy test for females of child bearing potential only
  - Biomarkers
- Dispense study drugs
- 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)

6.4.3. Week 8 Visit (±3 days)

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

Subjects should also be instructed to HOLD their dose of study drugs on the day of their Week 8 visit until all visit procedures have been completed. The study drugs should be taken after the visit.

The following will be performed and documented at these visits (±3 days):

- Symptom driven physical examination
- Record vital signs, and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
  - Single PK sampling
- Urine pregnancy test for females of child bearing potential only
- Dispense study drugs
- 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)

6.4.4. Week 12 Visit (±7 days)

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the Week 12 visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Subjects should also be instructed to HOLD their dose of study drugs on the day of their Week 12 visit until all visit procedures have been completed. The study drugs should be taken after the visit.

The following will be performed and documented at this visit (±7 days):

- QoL Questionnaires (SF-36, WPAI, and CLDQ)
- Symptom driven physical examination

- Record vital signs, waist circumference, and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile
  - Hemoglobin A1c
  - Biomarker
  - Single PK sampling
- Collect urine samples for:
  - Urine pregnancy test for females of child bearing potential only
  - Biomarkers
- Conduct standard 12-Lead ECG
- Perform FibroScan® (if available)
- Perform MRE and MRI-PDFF
- Collect stool sample for Biomarkers (see Study Reference Binder for instructions)
- 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)

6.4.5. Unscheduled Visit

Additional unscheduled assessments may be performed at the discretion of the investigator.

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

Subjects should also be instructed to HOLD their dose of study drugs on the day of an unscheduled visit until all visit procedures have been completed. The study drugs should be taken after the visit.

At a minimum, the following will be performed and documented.

- Symptom driven physical examination
- Obtain blood samples for:
  - Chemistry
  - Hematology
- Record 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.

6.4.6. Follow-Up Visit (±5 days)

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

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 under fasting condition the next morning.

The following will be performed and documented at this visit (±5 days):

- Symptom driven physical examination
- Record vital signs, and body weight
- Obtain blood samples for:
  - Chemistry
  - Hematology
  - Coagulation Panel
  - Lipid Profile

- Urine pregnancy test for female subjects of child bearing 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. Assessments for Premature Discontinuation from Study

Subjects prematurely discontinuing from the study (for example, as a result of an AE), should have an Early Termination (ET) visit, if possible, and a Follow-Up visit 4 weeks after the date of last dose of study drugs. The study assessments to be performed at the ET visit are the same as those performed at the Week 12 visit (refer to Section 6.4.4). The study assessments to be performed at the Follow-Up visit are listed in Section 6.4.6. The subject will then be withdrawn from the study.

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

6.6. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- 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 request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 3.
- Sponsor discretion
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.7. CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted].

6.8. Description of Assessments

6.8.1. Clinical Laboratory Analytes

Fasting is required prior to all study visits. All study procedures will be performed before dosing while the subject is in a fasted state. Subjects will take their dose of study drugs after the study visit has concluded.

Chemistry:

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase (ALP), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, gamma-glutamyl transferase (GGT). Also includes C-Peptide and Insulin for the Baseline/Day1, Week 4, and 12 visits.

Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft 1976} using actual body weight (BW). The calculation will be performed by the central laboratory.

Hematology:

Hematocrit (Hct), Hemoglobin (Hb), Platelet count, Red blood cell count (RBC), White blood cell count (WBC) with differential (absolute and percentage) including Lymphocytes, Monocytes, Neutrophils, Eosinophils, and Basophils and, Reticulocyte count and mean corpuscular volume (MCV).

Coagulation Panel:

INR, Prothrombin time (PT), partial thromboplastin time (PTT)

Pregnancy Tests:

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

Additional Tests:

Lipid Profile, Hemoglobin A1c, HIV-1, HBV & HCV Serology (if HCV Ab positive, reflex to HCV RNA), urine drug screen (for amphetamines, cocaine, opiates), serumCCI [redacted] and genomic sample collection.

Biomarkers:

Including but not limited to: CK18 (M30 and M65), FGF19, C4, Apolipoprotein B (Apo B), metabolite profile, bile acids, stool microbiome, blood miRNA, NMR lipoprofile, free fatty acids, ELF™ Test, and FibroSURE/FibroTest®.

CCI [redacted].

Pharmacokinetic (PK) Assessments:

Single PK Sampling

Single PK samples will be collected and archived for PK analysis of GS-0976 and other metabolites as applicable

CCI [redacted]

[redacted]

6.8.2. Physical Examination

A complete physical examination 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 physical examination 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 hip circumference will be collected at specified time points.

6.8.3. 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 $\geq$ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;

Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

6.8.4. 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. If available, historical liver biopsy information will also be collected.

6.8.5. Pharmacogenomic Testing

From subjects who agree to participate and provide consent, one blood sample will be obtained. This sample should be collected at the Day 1 visit, but may be collected at any time during the study or at a separate poststudy visit, if necessary.

6.8.6. 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.

6.8.6.1. SF-36 Health Survey

The SF-36 Health Survey 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.

6.8.6.2. CLDQ

The CLDQ asks 29 questions related to liver disease to measure health related quality of life in subjects with chronic liver disease.

6.8.6.3. 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.

6.8.7. Electrocardiogram

Standard 12-lead electrocardiogram (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.

6.8.8. FibroScan®

The sites will perform liver stiffness assessments by FibroScan®. It is required that each subject have the FibroScan® assessments done with the same type of probe at Baseline Day 1 and Week 12 visits (if available).

6.8.9. MRE and MRI-PDFF

Liver stiffness will be assessed by MRE (shear wave 60 Hz) and the degree of steatosis will be measured by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF). These assessments can occur sequentially.

The MRE and MRI-PDFF images will be analyzed by a central reader.

Please refer to the Study Reference Binder for MRE and MRI-PDFF imaging guidelines.

6.9. End of Study Definition

Subjects are considered to have completed the study after the completion of the Week 16 Follow-Up visit, regardless of treatment duration or early termination of study drugs.

6.10. Poststudy Care

No poststudy ongoing care will be provided.

6.11. 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 AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or posttreatment complications that occur as a result of protocol specified procedures, 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 AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (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 preexisting and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

- **Yes**: There is reasonable possibility that the event may have been caused by the study drugs.

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

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

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

7.2.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, 4, or 5 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (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

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

7.3.1.1. Adverse Events

Following initiation of study medication until 30 days after last administration of study drugs, all AEs, regardless of cause or relationship must be reported to the eCRF database as instructed.

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

7.3.1.2. Serious Adverse Events

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

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of study drugs, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow-up period, however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drugs, he/she should promptly document and report the event to Gilead DSPH.

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

7.3.1.3. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH 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 DSPH 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 European Union (EU) Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to

expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

7.5. Toxicity Management

Observation for Drug Induced Liver Injury (DILI):

Although subjects randomized in this study will have baseline liver disease, their hepatic function should not be significantly impaired. However, at baseline, some may have liver biochemistry levels above the upper limit of normal (ULN).

For subjects with ALT and AST below ULN at study start, close observation for DILI (as described below) should be considered in subjects with any of the following criteria (all labs confirmed by repeat testing):

- ALT or AST > 3 x ULN at any time
- Total bilirubin > 2 x ULN
- ALP > 3 x ULN
- INR >1.5 x ULN (except for subjects on anticoagulant therapy)
- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%)

For subjects with ALT or AST between 1 and 5 x ULN at study start, close observation for DILI (as described below) should be considered in subjects with any of the following criteria (all labs confirmed by repeat testing):

- ALT or AST > 2 x baseline at any time
- Total bilirubin > 2 x ULN

- ALP > 3 x ULN
- INR >1.5 x ULN (except for subjects on anticoagulant therapy)
- Clinical signs or symptoms that are, in the opinion of the investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%).

Close observation includes:

- Repeating liver biochemistries (ALT, AST, ALP, total bilirubin, INR) within 48 hours
- 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 twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study drugs have been discontinued and subject is asymptomatic

During a period of close observation, study drugs can be continued, if desired, at the discretion of the principal investigator.

However, for all subjects, study drugs should be withheld if any of the following criteria are met:

- ALT or AST > 3 x ULN AND either Total bilirubin > 2 x ULN or INR > 1.5 (in subjects not on anticoagulation)
- ALT or AST > 3 x ULN AND the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks

AND

- No other cause for the combination of laboratory abnormalities is immediately apparent (e.g. prolonged INR with warfarin use) important potential causes or contributors to abnormal AST/ALT or total bilirubin values include, but are not limited to:
    - Obstructive gall bladder or bile duct disease

- Viral or alcoholic hepatitis (e.g. hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella)

- Autoimmune hepatitis

- Concomitant administration of other hepatotoxins, including excessive doses of acetaminophen, drugs that inhibit bilirubin glucuronidation (e.g. indinavir, atazanavir, irinotecan), or herbal or dietary supplements

- Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right-sided heart failure

- Wilson disease

- Progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST/ALT elevations)

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

Treatment-emergent toxicities will be noted by the Investigator and brought to the attention of the Medical Monitor. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed. Other than in the case of the liver enzymes noted above, Grade 3 or 4 clinically significant laboratory 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. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. Any questions regarding toxicity management should be directed to the Medical Monitor.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH by transmitting electronically and also by sending paper pregnancy report form within 24 hours of becoming aware of the pregnancy.

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH 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 DSPH. Gilead DSPH 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 DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject 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 DSPH, 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 special situations reports (SSRs) will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Special Situations Report (eSSR) Reporting Process

- Site personnel record all SSR data in the eCRF database and from there transmit the SSR information to Gilead DSPH 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 SSR information electronically, i.e., the eCRF database is not functioning, record the SSR on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead DSPH: Email: PPD
Fax: PPD

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

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

These reports must consist of situations that involve study drugs and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

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

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE 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

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

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-0976 in subjects with NASH.

The exploratory objectives of this study are as follows:

8.1.2. Primary Endpoint

The primary endpoint is the safety of GS-0976 in subjects with NASH.

8.1.3. Exploratory Efficacy Endpoints

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8.2. Analysis Conventions

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

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis is defined as the Full Analysis Set (FAS), which includes all subjects who were randomized into the study and received at least 1 dose of study drugs.

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

8.2.1.2. Safety

The primary analysis set for safety analyses is defined as all subjects who received at least one dose of study drugs. Subjects who receive study drugs other than that to which they were assigned for the entire duration of treatment, will be analyzed according to the study drugs received.

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

8.2.1.3. Pharmacokinetics

There are two pharmacokinetic analysis sets: 1) The PK analysis set which includes concentration data from the single samples drawn at each visit CCI [redacted]

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 GS-0976 (and its metabolites as applicable) are available. The PK analysis set will be used for analyses of population PK.

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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 (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities.

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

8.4. 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, body mass index, and randomization stratification group (presence or absence of diabetes), and other disease characteristic variables.

8.5. Efficacy Analysis

The biological activity of GS-0976 will be evaluated using radiologic and biochemical endpoints and biomarker variables. Because efficacy endpoints will be evaluated for exploratory purpose, formal statistical comparisons will not be made for these endpoints. Point estimates and ninety-five percent confidence intervals (95% CI) will be provided if applicable.

8.6. Safety Analysis

All safety data collected on or after the date that GS-0976 was first dispensed up to the date of last dose of GS-0976 plus 30 days will be summarized by treatment group. Data for the pretreatment and follow-up periods will be included in data listings.

8.6.1. Extent of Exposure

Data for a subject's extent of exposure to GS-0976 will be generated from the study drug administration eCRF. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database. Adverse event severity will be graded using the CTCAE Version 4.03.

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

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

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).

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme in the CTCAE Version 4.03 (refer to Appendix 4). Grading of laboratory abnormalities for analysis purposes will be performed by the central laboratory.

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

8.6.4. Other Safety Evaluations

The number and percentage of subjects developing antibodies to GS-0976 will be summarized by treatment arm. Summary statistics for the 12-lead ECGs performed at Baseline and Week 12 will be generated.

8.7. Pharmacokinetic Analysis

Plasma concentrations and pharmacokinetic parameters (eg, AUC_{tau}, C_{max} and C_{tau}) will be listed and summarized as appropriate for GS-0976 (and its metabolites as applicable) using descriptive statistics.

Details of the analysis plan will be provided in the pharmacokinetic reporting and analysis plan.

8.8. Biomarker Analysis

Descriptive statistics of biomarker expression and change from baseline will be provided at each sampling time by treatment. Point estimates and 95% confidence intervals may be calculated.

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8.9. Sample Size

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar

proof of concept studies. However, assuming that 4% of subjects in the placebo arm (N=25) and 32% in the GS-0976 20 mg arm (N=50) have a ≥ 30% reduction in MRI-PDFF at Week 12, this sample size will provide 80% power to detect the difference based on a two-sided Fisher's exact test at a significance level of 0.05.

8.10. Data Monitoring Committee

An independent, external data monitoring committee (DMC) that consists of two hepatologists and a PhD statistician will review the progress of the study and perform reviews of safety data. The DMC will convene once 20 subjects have been randomized and will meet every 3 to 4 months thereafter to monitor the study for safety events. The DMC will meet on an ad hoc basis if there are at least 3 similar Grade ≥ 3 serious, treatment related Common Terminology Criteria for Adverse Events (CTCAE) observed in the trial. In the event of two similar Grade 4-CTCAE treatment related events or one Grade 5-CTCAE treatment related event, the DMC will review the data and advise the sponsor regarding stopping or continuing the trial. The DMC will provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

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

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

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), 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. The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, “Responsibilities of Sponsors and Investigators,” 21 CFR, part 50, "Protection of Human Subjects", and 21 CFR, part 56, "Institutional Review Boards".

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, "Financial Disclosure by Clinical Investigators", providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the study drugs 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 (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. The investigator will not begin any study subject activities until approval from the IRB has been documented and provided as a letter to the investigator.

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

9.1.3. 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-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 local requirements. The consent form will inform subjects about sample retention.

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, 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 randomized 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 study drugs, 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, eCRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not randomized

- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drugs, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject randomized, 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 and the subject has been randomized. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as

well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g., data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Study Drug Accountability and Return

Gilead recommends that used and unused study drug supplies be returned to the shipping facility from which it came 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 study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB, 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 in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.2.2. Study Report

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.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Monitoring and Oversight of Biomarker Specimens

Biomarker research specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form.

9.3.4. 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.

9.3.5. 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, and ECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGEMENT

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-0976 in Subjects with Nonalcoholic Steatohepatitis

GS-US-426-3989, Amendment 1, 15 December 2016

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

PPD

Medical Monitor

PPD

16 December 2016
Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table for GS-US-426-3989

Assessments	Screening[a]	Baseline / Day 1	On-treatment Visits				Follow Up Visit[b] (± 5 Days)
			Week 1 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 12/ET[b] ± 7 days	
Clinical Assessments							
Written Informed Consent[c]	X						
Determine Eligibility	X	X					
Medical History	X						
Historical Liver Biopsy (If Available)	X						
Physical Examination	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Vital Signs[e] including Weight	X	X	X	X	X	X	X
Height	X						
Waist Circumference		X				X	
12- lead ECG	X	X				X	
Ultrasound[f]	X						
MRE, MRI-PDFF	X					X	
FibroScan®[g]		X				X	
SF-36, WPAI, and CLDQ Questionnaires[h]		X				X	
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Dispense Study Drugs		X		X	X		
Review of Study Drug Dosing Compliance (Pill Count)			X	X	X	X	
Laboratory Assessments							
Subject Fasting[i]	X	X	X	X	X	X	X

Assessments	Screening[a]	Baseline / Day 1	On-treatment Visits				Follow Up Visit[b] (± 5 Days)
			Week 1 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 12/ET[b] ± 7 days	
Chemistry, Hematology, Coagulation Panel	X	X	X	X	X	X	X
Lipid Profile		X	X	X	X	X	X
Pregnancy Test[j]	X	X		X	X	X	X
Serum FSH[k]	X						
Single PK Sampling			X	X	X	X	
Hemoglobin A1c	X	X				X	
Blood and Urine Collection (Biomarker)		X	X	X		X	
Stool Collection (Biomarker)		X				X	
Urine Drug Screening[l]	X						
HIV-1, HBV & HCV[m] Serology	X						
CCI							
Genomic Sample[n]		X					

a. Screening assessments to be completed within 6 weeks prior to Day 1. The Screening period also may be extended longer under special circumstances with the explicit approval of the Gilead Medical Monitor.
b. Subjects discontinuing treatment at any time for any reason (Early Termination – ET) should complete the procedures listed for the Week 12/ET visit AND the Follow-Up visit.
c. Obtain written informed consent before initiation of any screening procedure.
d. Symptom-driven physical examination
e. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
f. Ultrasound may be performed if necessary to confirm NAFLD.
g. Perform FibroScan® if available.
h. It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the subject seeing a health care provider. Refer to the Study Reference Binder for guidance on QoL questionnaire administration for subjects with QoL questionnaires available at Baseline/Day 1.
i. Subjects must be in a fasted state at least 8 hours prior to blood collection.
j. Females of childbearing potential only (See Appendix 3). Serum pregnancy test at Screening and urine pregnancy test at all other visits, except Week 1.
k. CCI
l. Drug screen for amphetamines, cocaine, and opiates (i.e., heroin, morphine).
m. HCV Ab positive, reflex to HCV RNA.
n. CCI

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

1) Definitions

a. Definitions 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. Definitions 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) Contraceptive Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

The data of GS-0976 on pregnant women is not available now. Relevant non-clinical reproductive toxicity studies for human pregnancy have not been conducted yet. There are insufficient data to exclude the possibility of a clinically relevant interaction between GS-0976 and hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the investigator's brochure for GS-0976 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 not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the check-in visit prior to enrollment. At minimum, a pregnancy test will be performed at the end of relevant system exposure. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular

periods. Female subjects must agree to one of the following from Screening until 30 days following the last dose of the study drugs.

- 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)

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 the study drugs.

3) Contraceptive Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until 90 days after the last dose of the study drugs.

Male subjects must refrain from sperm donation from clinic admission, throughout the study period, and continuing for at least 90 days following the last dose of study drugs.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicide 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 (90 days of partner of male subject) 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 drugs immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf