CLINICAL STUDY PROTOCOL

Study Title:	A Proof of Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Regimens in Subjects with Nonalcoholic Steatohepatitis (NASH)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	141683
Clinical Trials.gov Identifier:	NCT02781584
Indication:	Nonalcoholic steatohepatitis (NASH)
Protocol ID:	GS-US-384-3914
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 13 April 2016 Amendment 1: 19 May 2016 Amendment 2: 14 July 2016 Amendment 3: 07 October 2016 Amendment 4: 22 December 2016 Amendment 5: 22 February 2017 Amendment 6: 28 April 2017 Amendment 7: 05 June 2017 Amendment 8: 03 November 2017 Amendment 9: 14 June 2018 Amendment 10: 13 July 2018 Amendment 11: 26 September 2018 Amendment 12: 11 September 2019

TABLE OF CONTENTS

LIST OF APPENDIX TABLES

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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

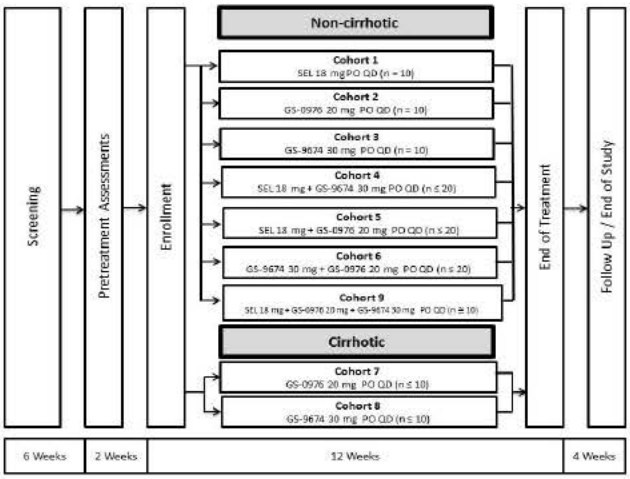
Study Title:	A Proof of Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Regimens in Subjects with Nonalcoholic Steatohepatitis (NASH)
IND Number:	141683
Clinical Trials.gov Identifier:	NCT02781584
Study Centers Planned:	Approximately 10 centers in the United States and New Zealand
Number of Subjects Planned:	Approximately 230 Subjects
Target Population:	Males and non-pregnant, non-lactating females between 18-75 years (Cohorts 1-9) and ≥18 years (Cohorts 10-13) of age with NAFLD/NASH.
Duration of Treatment:	Up to 24 weeks
Duration of Study:	Participation in the study can last up to 36 weeks, which includes up to a 6-week screening period, a 2-week pretreatment assessment period, up to a 24-week treatment period, and up to a 4-week follow-up period
Objectives:	The primary objective of this study is as follows: To evaluate the safety and tolerability of study drug(s) in subjects with NAFLD/NASH. CCI [redacted] [redacted] [redacted]

[redacted]

Study Design:

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

For Cohorts 1 through 9, eligible subjects will be enrolled to receive treatment with selonsertib (SEL; GS-4997), GS-0976, GS-9674; the combination of SEL and GS-9674, SEL and GS-0976, GS-9674 and GS-0976; or SEL, GS-0976 and GS-9674 for 12 weeks as shown in the figure below.



Approximately 230 subjects total will be enrolled into one of 13 cohorts:

Cohort 1 (SEL) will consist of 10 enrolled subjects

Cohort 2 (GS-0976) will consist of 10 enrolled subjects

Cohort 3 (GS-9674) will consist of 10 enrolled subjects

Cohort 4 (SEL + GS-9674) will consist of up to 20 enrolled subjects

Cohort 5 (SEL + GS-0976) will consist of up to 20 enrolled subjects

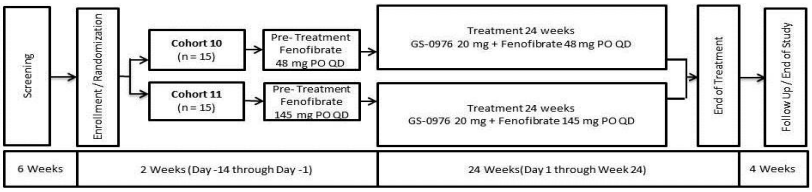
Cohort 6 (GS-9674 + GS-0976) will consist of up to 20 enrolled subjects

Cohort 7 (GS-0976) will consist of up to 10 enrolled subjects with Child-Pugh-Turcotte Class A (CPT A) cirrhosis

Cohort 8 (GS-9674) will consist of up to 10 enrolled subjects with CPT A cirrhosis

Cohort 9 (SEL + GS-0976 + GS-9674) will consist of approximately 10 enrolled subjects.

For Cohorts 10 and 11, eligible subjects will be randomized to receive pretreatment with fenofibrate 48 mg or fenofibrate 145 mg from Day -14 to Day -1 and will be treated with GS-0976 20 mg and fenofibrate 48 mg or GS-0976 20 mg and fenofibrate 145 mg for 24 weeks as shown in the figure below.

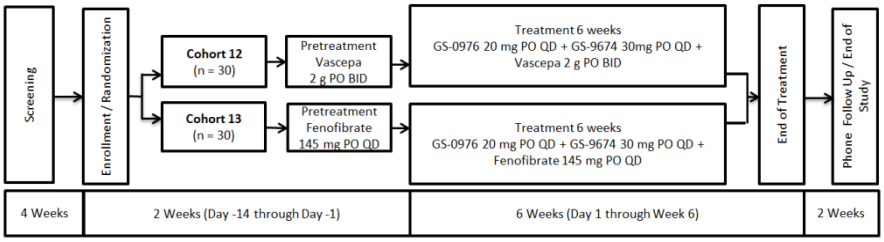


Approximately 30 subjects will be randomized (1:1) into either Cohorts 10 or 11. Randomization will be stratified by (1) screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]), and (2) fibrosis stage [F3 defined by liver biopsy or screening MRE with liver stiffness < 4.67 kPa or F4 defined by liver biopsy or screening MRE with liver stiffness ≥ 4.67 kPa. Approximately 60% of subjects in each cohort should have cirrhosis (F4) based on Inclusion Criteria 5. Approximately 60% subjects in each cohort should have screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL as below:

- Cohort 10 (GS-0976 20 mg + fenofibrate 48 mg) will consist of 15 subjects:
  - Approximately 9 subjects with Screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL
  - Approximately 6 subjects with Screening serum triglycerides ≥ 250 mg/dL and < 500 mg/dL

- Cohort 11 (GS-0976 20 mg + fenofibrate 145 mg) will consist of 15 subjects:
  - Approximately 9 subjects with Screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL
  - Approximately 6 subjects with Screening serum triglycerides ≥ 250 mg/dL and < 500 mg/dL

For Cohorts 12 and 13, eligible subjects will be randomized to receive pretreatment with Vascepa® 2 g twice daily or fenofibrate 145 mg once daily from Day -14 to Day -1 and will be treated with GS-0976 20 mg once daily, GS-9674 30 mg once daily, and Vascepa® 2 g twice daily; or GS-0976 20 mg once daily, GS-9674 30 mg once daily, and fenofibrate 145 mg once daily for 6 weeks as shown in the figure below.



Approximately 60 subjects will be randomized (1:1) into either Cohorts 12 or 13. Randomization will be stratified by screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]).

- Cohort 12 (GS-0976 20 mg once daily + GS-9674 30 mg once daily + Vascepa® 2 g twice daily) will consist of 30 subjects
- Cohort 13 (GS-0976 20 mg once daily + GS-9674 30 mg once daily + fenofibrate 145 mg once daily) will consist of 30 subjects

Diagnosis and Main Eligibility Criteria:

Key Inclusion Criteria:

1. Males and females between 18-75 years (Cohorts 1-9) and ≥ 18 years (Cohorts 10-13) of age; inclusive based on the date of the Screening Visit;
2. Willing and able to provide informed consent prior to any study specific procedures being performed;
3. For Cohorts 1 through 6 and 9, subjects must meet all of the following conditions (a-d OR e&f):
   a) Clinical diagnosis of nonalcoholic fatty liver disease (NAFLD),

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

c) Screening MRI-PDFF with ≥ 10% steatosis,

d) Screening MRE with liver stiffness ≥ 2.88 kPa,

OR

e) A historical liver biopsy within 12 months of Screening consistent with NASH (defined as the presence of steatosis, inflammation, and ballooning) with stage 2-3 fibrosis according to the NASH Clinical Research Network (CRN) classification (or equivalent),

AND

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

4. For Cohorts 7 and 8, subjects must have a clinical diagnosis of NAFLD and have at least one of the following criteria (a-d):

   a) Screening MRE with liver stiffness ≥ 4.67 kPa,

   b) A historical FibroScan® ≥ 14 kPa within 6 months of Screening,

   c) Screening FibroTest® ≥ 0.75,

   d) A historical liver biopsy consistent with stage 4 fibrosis according to the NASH CRN classification (or equivalent);

5. For Cohorts 10 and 11, subjects must have a clinical diagnosis of NAFLD and the following criteria:

   a) At least two criteria for metabolic syndrome modified from the NCEP ATP III Guidelines, at Screening:

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

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

      iii. Fasting triglycerides ≥ 150 mg/dL,

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

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

AND one of the following criteria:

b) A historical liver biopsy within 6 months of Screening consistent with NASH and bridging fibrosis (F3) or within 12 months of Screening consistent with NASH and compensated cirrhosis (F4) in the opinion of the investigator,

c) Screening liver stiffness by MRE ≥ 3.64 kPa,

d) Screening liver stiffness by FibroScan® ≥ 9.9 kPa;

6. For Cohorts 12 and 13, subjects must have a clinical diagnosis of NAFLD/NASH and the following criteria:

   a) At least two criteria for metabolic syndrome modified from the NCEP ATP III Guidelines, at Screening:

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

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

      iii. Fasting triglycerides ≥ 150 mg/dL,

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

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

   OR one of the following criteria:

   b) A historical liver biopsy within 6 months of Screening consistent with NASH for subjects without compensated cirrhosis (F4); or within 12 months of Screening consistent with NASH for subjects with compensated cirrhosis (F4) in the opinion of the investigator,

   c) A historical MRE with liver stiffness ≥ 2.88 kPa within 6 months of Screening,

   d) A historical FibroScan® with liver stiffness ≥ 9.9 kPa within 6 months of Screening,

   AND

   e) No documented weight loss > 5% between the date of the historical liver biopsy, historical MRE, or historical FibroScan® and Screening;

7. Platelet count ≥ 100,000/µL;

8. Serum creatinine < 2 mg/dL (Cohorts 1-9) at Screening;

9. Estimated glomerular filtration rate (eGFR) ≥ 80 mL/min

(Cohorts 10-11) or ≥ 60 mL/min (Cohorts 12-13), as calculated by the Cockcroft-Gault equation at Screening;

10. For Cohorts 10-13, serum triglyceride level ≥ 150 mg/dL at Screening.

Key Exclusion Criteria:

1. Pregnant or lactating females;
2. Other causes of liver disease including autoimmune, viral, and alcoholic liver disease;
3. Any history of decompensated liver disease, including ascites, hepatic encephalopathy, or variceal bleeding;
4. For Cohorts 7-8 and 10-13, Child-Pugh-Turcotte (CPT) score > 6 (Appendix 4) at Screening, unless due to an alternative etiology such as Gilbert's syndrome or therapeutic anticoagulation;
5. History of liver transplantation;
6. History of hepatocellular carcinoma;
7. Weight reduction surgery in the past 2 years or planned during the study;
8. Documented weight loss > 5% between the date of the historical liver biopsy and Screening, if applicable;
9. Body Mass Index (BMI) < 18 kg/m^2;
10. ALT > 5 x ULN at Screening;
11. For Cohorts 10-13, HbA1c ≥ 9.5% (or serum fructosamine ≥ 381 µmol if HbA1c is unable to be resulted) at Screening;
12. For Cohorts 10-13, hemoglobin ≤ 10.6 g/dL at Screening;
13. INR > 1.2 (Cohorts 1-9) or INR > 1.4 (Cohorts 10-13) at Screening, unless on anticoagulation therapy;
14. Total bilirubin > 1x ULN (Cohorts 1 through 6 and 9), >1.5 x ULN (Cohorts 7 and 8), or >1.3 x ULN (Cohorts 10-13) except in confirmed cases of Gilbert's syndrome;
15. Triglycerides ≥ 500 mg/dL (Cohorts 5-8 and 10-13) or ≥ 250 mg/dL (Cohort 9) at Screening;
16. Model for End-Stage Liver Disease (MELD) score > 12 at Screening (Cohorts 10 -13), unless due to an alternate etiology such as therapeutic anticoagulation;
17. Chronic hepatitis B (HBsAg positive);
18. Chronic hepatitis C (HCV RNA positive). Subjects cured of HCV infection less than 2 years prior to the Screening visit are not eligible (Cohorts 10-13);

19. HIV Ab positive;
20. Presence of gallstones within 6 months of Screening (Cohorts 10-13);
21. Alcohol consumption greater than 21 oz/week for males or 14 oz/week for females (1oz/30 mL of alcohol is present in 1 12oz/360 mL beer, 1 4oz/120 mL glass of wine, and a 1 oz/30 mL measure of 40% proof alcohol);
22. 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;
23. Unstable cardiovascular disease;
24. History of intestinal resection of the extent that would result in malabsorption;
25. Use of any prohibited concomitant medications as described in Section 5.8;
26. History of a malignancy within 5 years of Screening with the following exceptions:
    a) Adequately treated carcinoma in situ of the cervix,
    b) Adequately treated basal or squamous cell cancer or other localized non-melanoma skin cancer.

Study Procedures/ Frequency:

After signing the informed consent form, subjects will complete a Screening Visit which will include the following assessments: complete medical history with review of historical liver biopsy obtained within the last 12 months of Screening (date of initial informed consent) for noncirrhotics and at any time for cirrhotics, to assess subject eligibility for Cohorts 1-9. For Cohorts 10-11, review of the historical liver biopsy obtained within the last 6 months of Screening (date of initial informed consent) for subjects with bridging fibrosis (F3) and within the last 12 months for subjects with cirrhosis (F4), to assess subject eligibility (if applicable). For Cohorts 12-13, review of historical liver biopsy within 6 months of Screening (date of initial informed consent) consistent with NASH for subjects without compensated cirrhosis (F4); or within 12 months of Screening consistent with NASH for subjects with compensated cirrhosis (F4), or review of historical MRE and/or FibroScan® obtained within the last 6 months of Screening (date of initial informed consent), to assess subject eligibility (if applicable). Other assessments include complete physical examination (PE) including height, CCI [redacted], and vital signs; laboratory assessments; serum

pregnancy test (for females of childbearing potential); CCI [redacted] blood collection for ELF™ Test CCI [redacted] standard 12-lead electrocardiogram (ECG); CCI [redacted] (Cohorts 10-11); adverse events (AE) related to Screening procedures; concomitant medications; and CCI [redacted]

Subjects determined to be eligible for the study based on the inclusion/exclusion criteria will then begin Cycle 1 of the Kinetic Biomarkers (Cohorts 1-11). CCI [redacted] For Cohorts 1-9 subjects will complete two additional cycles of Kinetic Biomarkers from Day 14 through Day 20 (Cycle 2) and Day 70 through Day 76 (Cycle 3). For Cohorts 10-11, subjects will complete two additional cycles of Kinetic Biomarkers from Day 70 through Day 76 (Cycle 2) and Day 154 through Day 160 (Cycle 3).

All Cohort 1-11 subjects enrolled in the study will complete the Kinetic Biomarker studies. The first dose of 50 mL deuterated water will be administered under the supervision of investigative site personnel and monitored for at least 30 minutes after for any side effects.

For Cohorts 1 through 9, eligible subjects will be enrolled to receive treatment with SEL, GS-0976, GS-9674; the combination of SEL and GS-9674, SEL and GS-0976, GS-9674 and GS-0976; or SEL, GS-0976 and GS-9674 for 12 weeks. For Cohorts 10-11, eligible subjects will be randomized to receive pretreatment with fenofibrate from Day -14 to Day -1 and receive treatment with GS-0976 and fenofibrate from Day 1 through 24 weeks.

For Cohorts 12-13, eligible subjects will be randomized to receive pretreatment with Vascepa® or fenofibrate from Day -14 to Day -1 and receive treatment with GS-0976 and GS-9674 and Vascepa® or fenofibrate from Day 1 through Week 6.

Pretreatment and Treatment study assessments will include:

- Confirmation of eligibility at Day -14
- Medical history at Day -14 (Cohorts 10-13) and Day 1 (Cohorts 1-11)
- Symptom driven PE, vital signs, and weight at
  - Day 1 and Weeks 1, 4, 8, 12 (Cohorts 1-9)
  - Days -14, 1 and Weeks 1, 4, 8, 12, 16, 24 (Cohorts 10-11)
  - Days -14, 1 and Weeks 4, 6 (Cohorts 12-13)

CCI [redacted]

CCI [redacted]

- Standard 12-lead ECG at
  - Week 12 (Cohorts 1-9)
  - Weeks 12, 24 (Cohorts 10-11)
  - Week 6 (Cohorts 12-13)
- Chemistry, hematology, and coagulation panel at
  - Day 1 and at Weeks 1, 4, 8, 12 (Cohorts 1-9)
  - Days -14, -11, -7, 1 and Weeks 1, 4, 8, 12, 16, 24, 28 (Cohorts 10-11)
  - Days -14, 1 and Weeks 4, 6 (Cohorts 12-13)
- Pregnancy testing (females of childbearing potential only) at
  - Day 1 and at Weeks 4, 8, 12 (Cohorts 1-9)
  - Day 1 and Weeks 4, 8, 12, 16, 22, and 24 (Cohorts 10-11)
  - Days -14, 1 and Weeks 4, 6 (Cohorts 12-13)
- Biomarker Testing
  - CCI [redacted]
  - [redacted]
  - CCI [redacted]
  - [redacted]
  - CCI [redacted]
  - [redacted]
  - CCI [redacted]
  - [redacted]

[redacted]

- Apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and NMR Lipoprofile collection at
  - Day 1 and at Weeks 1, 4, 8, 12 (Cohorts 1-9)
  - Days -14, 1 and Weeks 1, 4, 8, 12, 16, 24 (Cohorts 10-11)
  - Days -14, 1 and Weeks 4, 6 (Cohorts 12-13)
- Total bile acids at
  - Day 1 and at Weeks 1, 4, 8, 12 (Cohorts 1-9)
  - Days -14, 1 and Weeks 1, 4, 8, 12, 16, 24 (Cohorts 10-11)
- Beta-hydroxybutyrate and adiponectin collection at
  - Day 1 and Weeks 4, 12 (Cohorts 1-9)
  - Days -14, 1 and Weeks 12, 24 (Cohorts 10-11)
- hsCRP at
  - Days -14, 1 and Weeks12, 24 (Cohorts 10-11)

[redacted]

- Genomic sample collection at Day 1 (Cohorts 1-13)

[redacted]

- Hemoglobin A1c (HbA1c) at
  - Day 1 and Week 12 (Cohort 1-9)
  - Day -14, 1 and Weeks 12, 24 (Cohorts 10-11)
  - Day 1 (Cohorts 12-13)
- Quality of Life (QoL) questionnaires at
  - Day 1 and Week 12 (Cohorts 1-9)
  - Day 1 and Week 12, 24 (Cohorts 10-11)

Kinetic Biomarker Assessments (Cohorts 1-11)

Cycle 1

Subjects will drink 50 ml of deuterated water three times per day starting on Day -14 through Day -8.

Plasma Collection

Blood will be collected at Day -14, Day -11, Day -7, Day 1 and Day 7 (Cohorts 1-11).

Urine Collection

Urine will be collected on Day -14, Day -11, Day -7, Day 1 (Cohorts 1-11) and Day 7 (Cohorts 4-11).

Saliva Collection

Saliva will be collected on Day 7(Cohorts 1-3).

Cycle 2

Subjects will drink 50 ml of deuterated water three times per day starting on Day 14 through Day 20 (Cohorts 1-9) and on Day 70 through Day 76 (Cohorts 10-11).

Plasma Collection

Blood will be collected at Day 14, Day 17, Day 21, and Day 28 (Cohorts 1-9) and Day 56, Day 70, Day 73, Day 77 , Day 84 and Day 126 (Cohorts 10-11).

Urine Collection

Urine will be collected on Day 14, Day 17, Day 21, and Day 28 for (Cohorts 1-9) and Day 56, Day 70, Day 73, Day 77, Day 84 and Day 126 for (Cohorts 10-11).

Saliva Collection

Saliva will be collected on Day 35 for (Cohorts 1-3).

Cycle 3

Subjects will drink 50 ml of deuterated water three times per day starting on Day 70 through Day 76 (Cohorts 1-9) and on Day 154 through Day 160 (Cohorts 10-11).

Plasma Collection

Blood will be collected at Day 70, Day 73, Day 77, and Day 84 (Cohorts 1-9) Day 154, Day 157, Day 161 and Day 168 (Cohorts 10-11).

Urine Collection

Urine to be collected on Day 70, Day 73, Day 77, and Day 84 (Cohorts 1-9) and Day 154, Day 157, Day 161, and Day 168 (Cohorts 10-11).

Saliva Collection

Saliva will be collected on Day 91 (Cohorts 1-3).

Subjects will return for their final visit 4 weeks after the Week 12 visit (Week 16) (Cohorts 1-9), or 4 weeks after the Week 24 visit (Week 28) (Cohorts 10-11). At this visit, subjects will have a symptom driven PE, vital signs, CCI [redacted], review of concomitant medications and AEs, and blood will be drawn for hematology, blood chemistry, and a coagulation panel. A urine pregnancy test will be performed for females of childbearing potential only.

For Cohorts 12 and 13, subjects will have a Follow-up Phone Visit two weeks after last dose of study drug. At this visit, a review of concomitant medications and AEs will be completed, and a urine pregnancy test will be performed for females of childbearing potential only.

Test Product:

For Cohorts 1, 4, 5 and 9, SEL will be supplied as round, plain-faced, white film-coated tablets containing 18 mg of SEL. In addition to the active ingredient, SEL tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide and talc.

For Cohort 2, GS-0976 will be supplied as white opaque size 0 hard gelatin capsules containing 10 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.

For Cohorts 5-7 and 9-13, GS-0976 will be supplied as round, plain-faced, film coated white tablets containing 20 mg of GS-0976. In addition to the active ingredient, GS-0976 tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc, which are common pharmaceutical excipients.

For Cohort 3, GS-9674 will be supplied as round, plain-faced, film-coated orange tablets containing 10 mg (as free form equivalent) of GS-9674. In addition to the active ingredient, GS-9674 tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium stearate, and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide and ferrosoferric oxide.

For Cohorts 4, 6, 8 and 9, GS-9674 will be supplied as round, plain-faced, film-coated orange tablets containing 30 mg (as free form equivalent) of GS-9674. In addition to the active ingredient, GS-9674 tablets contain the following inactive ingredients: microcrystalline cellulose, mannitol, crospovidone, magnesium stearate and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide and ferrosoferric oxide.

For Cohorts 12 and 13, GS-9674 will be supplied as round, film-coated green tablets, debossed with “GSI” on one side of the tablet and “30” on the other side of the tablet, and containing 30 mg (as free form equivalent) of GS-9674. In addition to the active ingredient, GS-9674 tablets contain the following inactive ingredients: microcrystalline cellulose, mannitol, crospovidone, magnesium stearate and film-coating material composed of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, and ferrosoferric oxide.

For Cohorts 10 and 11, fenofibrate will be supplied in 48 mg and 145 mg tablets. Commercially available fenofibrate will be used for the study. Information regarding the formulation of commercially available fenofibrate can be found in the prescribing information.

For Cohort 12, Vascepa® will be supplied in 1 g capsules, with two capsules to be taken two times daily. Commercially available Vascepa® will be used for the study. Information regarding the formulation of commercially available Vascepa® can be found in the prescribing information.

	For Cohort 13, fenofibrate will be supplied in 145 mg tablets. Commercially available fenofibrate will be used for the study. Information regarding the formulation of commercially available fenofibrate can be found in the prescribing information.
Dose, and Mode of Administration:	Cohort 1: SEL 18 mg (1 x 18 mg tablet) administered orally once daily Cohort 2: GS-0976 20 mg (2 x 10 mg capsules) administered orally once daily Cohort 3: GS-9674 30 mg (3 x 10 mg tablets) administered orally once daily Cohort 4: SEL 18 mg (1 x 18 mg tablet) + GS-9674 30 mg (1 x 30 mg tablet) administered orally once daily Cohort 5: SEL 18 mg (1 x 18 mg tablet) + GS-0976 20 mg (1 x 20 mg tablet) administered orally once daily Cohort 6: GS-9674 30 mg (1 x 30 mg tablet) + GS-0976 20 mg (1 x 20 mg tablet) administered orally once daily Cohort 7: GS-0976 20 mg (1 x 20 mg tablet) administered orally once daily Cohort 8: GS-9674 30 mg (1 x 30 mg tablet) administered orally once daily Cohort 9: SEL 18 mg (1 x 18 mg tablet) + GS-0976 20 mg (1 x 20 mg tablet) + GS-9674 30 mg (1 x 30 mg tablet) administered orally once daily Cohort 10: GS-0976 20 mg (1 x 20 mg tablet) + fenofibrate 48 mg (1 x 48 mg tablet) administered orally once daily Cohort 11: GS-0976 20 mg (1 x 20 mg tablet) + fenofibrate 145 mg (1 x 145 mg tablet) administered orally once daily Cohort 12: GS-0976 20 mg (1x 20 mg tablet) + GS-9674 (1x 30 mg tablet) administered orally once daily + Vascepa® 4 g (2 x 1 g capsule) administered orally two times daily Cohort 13: GS-0976 20 mg (1x 20 mg tablet) + GS-9674 (1 x 30 mg tablet) + fenofibrate 145mg (1 x 145 mg tablet) administered orally once daily

Criteria for Evaluation:

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

CCI [redacted]

Statistical Methods:

Primary Endpoint: The primary endpoint is the safety of study drug(s) in subjects with NAFLD/NASH.

CCI [redacted]

Efficacy Analysis:	The biological and histological activity of study drug(s) will be evaluated using radiologic endpoints and biomarker variables. Because efficacy endpoints will be evaluated for exploratory purpose, formal statistical comparisons will not be made for these endpoints. Descriptive statistics (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, and maximum) will be provided by treatment group.
CCI [redacted]	[redacted]
Safety Analysis:	Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous values by treatment group.
Pharmacokinetic Analysis:	CCI [redacted] relevant metabolite(s), as applicable, will be listed and summarized. CCI [redacted]
Kinetic Biomarker Analysis:	The kinetic biomarkers will be analyzed to evaluate the pharmacodynamic (PD) effects of study drug(s). The assessment will involve the analysis of DNL values; specifically, the change (absolute and relative) from baseline between the post-dose and pre-dose deuterated water loading periods.
Sample Size:	For Cohorts 1 to 9, 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. For Cohorts 10 to 11, we assumed that among subjects with baseline hypertriglyceridemia ≥150 mg/dL (60% with serum triglycerides ≥ 150 mg/dL and < 250 mg/dL and 40% with serum triglycerides ≥ 250 mg/dL and < 500 mg/dL), Grade 3-4 hypertriglyceridemia (>500 mg/dL) would be observed in 28% following treatment with GS-0976. Assuming that the co-administration of fenofibrate and GS-0976 will reduce the incidence of Grade 3-4 hypertriglyceridemia to <5%, a sample size of 15 in each of Cohorts 10 and 11 will provide 82% power to detect the reduction based on a one-sided exact test at a significance level of 0.05.

For Cohorts 12 and 13, we assumed that among subjects with baseline hypertriglyceridemia (serum triglycerides ≥ 150 mg/dL and < 500 mg/dL), GS-0976 20 mg + GS-9764 30 mg once daily treatment will lead to a mean increase in serum triglycerides of 60 mg/dL from baseline after 6 weeks of treatment. Assuming that the co-administration of Vascepa® or fenofibrate with GS-0976 20 mg + GS-9764 30 mg will mitigate this increase in serum triglycerides and that the standard deviation for serum triglycerides after 6 weeks of treatment is 120 mg/dL, a sample size of 30 subjects in each cohort will provide 85% power to detect any increase based on a one-sided t-test at a significance level of 0.05.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
%GMR	percent geometric mean ratio
ACC	acetyl-coA carboxylases
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ASK1	apoptosis signal-regulating kinase 1
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
AUROC	area under the receiver operating characteristic curve
β-hCG	beta human chorionic gonadotropin
BAP	Biomarker Analysis Plan
BCL-2	B-cell lymphoma 2
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BSEP	bile salt export pump
BUN	blood urea nitrogen
C4	7alpha-hydroxy-4-cholesten-3-one
CCl	[redacted]
CBC	complete blood count
Cc	cubic centimeter
CDHFD	choline-deficient, high-fat diet
CFR	Code of Federal Regulations
CI	confidence interval
c-Jun	c-Jun protein
CK18	cytokeratin 18
C_{last}	last observed quantifiable plasma/serum concentration of the drug
CLDQ	Chronic Liver Disease Questionnaire
CL_{renal}	renal clearance
CL_{ss}	steady state clearance
C_{max}	maximum observed plasma/serum concentration of drug

COL1A1	collagen type I alpha 1 chain
CPT	Child-Pugh-Turcotte
CPT A	Child-Pugh-Turcotte Class A
CRF	case report form
CRN	Clinical Research Network
CRO	contract research organization
CsA	Cyclosporine
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	lowest concentration at which a medication is present in the body
CXCL1	chemokine (C-X-C motif) ligand 1
CYP	cytochrome P450
CYP1A2	cytochrome P450 1A2
CYP2B6	cytochrome P450 2B6
CYP2C19	cytochrome P450 2C19
CYP2C8	cytochrome P450 2C8
CYP2D26	cytochrome P450 2D6
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
DAB	Dabigatran
DDI	drug-drug interaction
DHA	docosahexaenoic acid
DILI	Drug Induced Liver Injury
DKD	Diabetic Kidney Disease
dL	Deciliter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DNL	de novo lipogenesis
DRSP	Drospirenone
PVE	Pharmacovigilance and Epidemiology
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
Eg	Example
CCI	[redacted]
EPA	eicosapentaenoic acid
EU	European Union
FAS	Full Analysis Set

FDA	(United States) Food and Drug Administration
FGF19	fibroblast growth factor 19
FSH	follicle stimulating hormone
FXR	Farnesoid X Receptor
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GMP	Good Manufacturing Practice
GMR	geometric mean ratio
HA	hyaluronic acid
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
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HLT	high-level term
HLGT	high-level group term
CCI	[redacted]
HPAH	heritable pulmonary arterial hypertension
Hr	Hour
Hz	Hertz
IB	investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IL-1β	interleukin-1 beta
IL-6	interleukin-6
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
IRB	institutional review board
IRS1	insulin receptor substrate 1
IUD	intrauterine device

IV	Intravenous
IWRS	interactive web response system
JNK	c-Jun N-terminal kinase
Kg	Kilogram
kPa	Kilopascal
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLT	lower-level term
LPL	lipoprotein lipase
LSM	least squares mean
LXR	liver X receptor
µg	Microgram
MAPK	mitogen-activated protein kinase
MATE1	multidrug and toxin extrusion protein 1
MCP-1	monocyte chemoattractant protein-1
MCV	mean corpuscular volume
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minute
mL	Milliliter
Mm	Millimeter
mmHg	millimeter of mercury
MRP2	multidrug resistance-associated protein 2
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
mRNA	messenger ribonucleic acid
NAFLD	nonalcoholic fatty liver disease
NaNO2	sodium nitrite
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
Ng	Nanogram
ng*h	nanogram*Planck's constant
NMR	nuclear magnetic resonance
NOAEL	no observed adverse event level
NOEL	no-observed-effect level
NTCP	sodium-taurocholate cotransporting polypeptide
OATP	organic anion-transporting polypeptide

OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OATP2B1	organic anion transporting polypeptide 2B1
OCT1	organic cation transporter 1
OCT2	organic cation transporter 2
OSTα	organic solute transporter alpha
OSTβ	organic solute transporter beta
Oz	Ounce
p38	mitogen-activated protein kinase
PAH	pulmonary arterial hypertension
PAH-CTD	pulmonary arterial hypertension associated with connective tissue disease
PAI-1	plasminogen activator inhibitor type 1
PBC	primary biliary cirrhosis
PBMC	peripheral blood mononuclear cells
PD	Pharmacodynamics
PDGF	platelet-derived growth factor
PE	physical exam
P-gp	P-glycoprotein
pH	measure of the acidity
PIIINP	N-Terminal Propeptide of Type III Collagen
CCI	[redacted]
PO	by mouth
p-p38	phospho-p38
PRA	Pravastatin
PSC	primary sclerosing cholangitis
PSR	picrosirius red
PT	preferred term
PT	prothrombin time
PTT	partial prothrombin time
PVR	pulmonary vascular resistance
Q1	1st quartile
Q3	3rd quartile
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
ΔΔQTcF	time matched, baseline adjusted, placebo-corrected QTcF
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula

RHC	right heart catheterization
RIF	Rifampin
RNA	ribonucleic acid
ROS	reactive oxygen species
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEL	selonsertib (formerly known as GS-4997)
SF-36	Short Form (36) Health Survey
SIM	Simtuzumab
α–SMA	α-smooth muscle actin
SOC	System Organ Class
SOP	standard operating procedure
SREBP-1c	sterol regulatory element-binding transcription factor 1c
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	an estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TEAEs	treatment emergent adverse events
TESAE	treatment-emergent SAE
TIMP 1	tissue inhibitor of metalloprotease 1
TGF-β	transforming growth factor beta
T_{last}	last measured concentration
T_{max}	time (observed time point) of C_{max}
TNF-α	tumor necrosis factor alpha
TQT	thorough QT
TXNIP	thioredoxin interacting protein
UDP	uridine 5'-diphospho
UGT1A1	UDP glucuronosyltransferase family 1 member A1
ULN	upper limit of the normal range
US	United States
USPI	United States Product Inserts
VAS	visual analogue scale
VORI	Voriconazole
VLDL	very-large density lipoprotein
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment Questionnaire

1. INTRODUCTION

1.1. Background

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

NASH is primarily thought to occur as the result of the metabolic syndrome: the impact of obesity, hepatic insulin resistance, and dyslipidemia. Fatty liver, or simple steatosis, is not sufficient to cause liver injury; it is the presence of inflammation and hepatocellular injury on the background of steatosis that produces NASH and may result in the progression to cirrhosis and its complications including end-stage liver disease. The “2-hit” hypothesis of NASH suggests that in the setting of steatosis and metabolic dysfunction, increased oxidative stress and the generation of reactive oxygen species (ROS) likely mediate the inflammatory changes in the liver (steatohepatitis) with progressive liver fibrosis {Dowman 2010, Koek 2011, Rolo 2012, Sumida 2013}. The major pathways in NASH disease progression include those involved in metabolic dysfunction in the hepatocyte, activation of hepatic stellate cells, and activation and recruitment of macrophages leading to hepatic inflammation and fibrosis. Advanced fibrosis and cirrhosis are characterized by extensive collagen deposition and remodeling of the extracellular matrix. Additionally, there is evidence which suggests that lipotoxic intermediates of fatty acids likely contribute to the etiology of NASH {Neuschwander-Tetri 2010}.

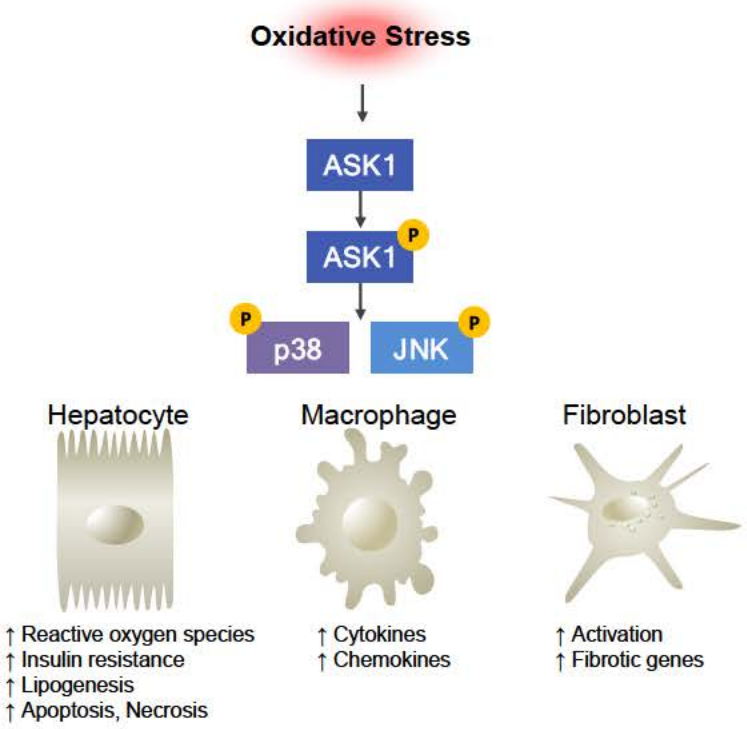
Over time, NASH may result in progressive liver fibrosis, ultimately resulting in cirrhosis. Advanced liver fibrosis (bridging fibrosis or cirrhosis) is associated with increased morbidity and mortality {Ekstedt 2014, Yeh 2014}. Cirrhosis increases the risk of developing hepatocellular carcinoma (HCC) and other complications of end-stage liver disease, including jaundice, fluid retention (edema and ascites), portal hypertension and variceal hemorrhage, impaired coagulation, and hepatic encephalopathy. Decompensated liver disease, as defined by the development of one of the above complications, has a high mortality rate and the only effective treatment is liver transplantation. With the increasing prevalence of obesity and obesity-related diseases, NASH is expected to become the leading indication for liver transplantation and the leading etiology of HCC among liver transplant recipients in the US {Afzali 2012, Wong 2014}.

1.2. General Information for Selonsertib

1.2.1. Selonsertib

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

Figure 1-1. ASK1 Signaling in NASH



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

1.2.2. Preclinical Pharmacology and Toxicology

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

Please refer to the SEL IB for additional details.

1.2.3. Clinical Trials of Selonsertib

As of 17 July 2019, 10 Phase 1, 6 Phase 2, and 3 Phase 3 clinical studies have been conducted/are ongoing in which 390 healthy subjects, 248 subjects with DKD, an estimated 40 subjects with CKD, 1473 subjects with NASH, 50 subjects with AH, and 145 subjects with PAH have been dosed with SEL.

Information on the ongoing or completed Phase 1 and 2 clinical studies can be found in the IB.

1.3. General Information for GS-0976

1.3.1. 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 nonalcoholic steatohepatitis (NASH) under IND 124915.

For further information on GS-0976, refer to the current IB for GS-0976.

1.3.2. 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 reduce the DNL, hepatic steatosis, insulin resistance, and fibrosis produced in nonclinical models of metabolic disease and fibrosis without affecting food consumption or markers of liver function.

As described in the IB, GS-834356, a liver-targeted ACC inhibitor and analogue of GS-0976, reduced steatosis in a murine model of NASH induced by a diet enriched in fat, cholesterol, and fructose (Fast food diet, FFD). ACC inhibition by GS-834356 dose-dependently reduced hepatic steatosis, liver triglycerides and cholesterol, plasma ALT and AST, and markers of hepatic fibrosis, but also dose-dependently increased plasma triglycerides in this model. GS-834356 also decreased hepatic triglycerides and increased plasma triglycerides in a rat high fat, high sucrose model of hepatic steatosis. These findings are consistent with a recent report that pharmacologic or genetic inhibition of ACC in the liver decreases hepatic triglyceride levels and increases plasma triglyceride levels {Goedeke 2018, Hertz 1995, Kim 2017}.

In high fat, high sucrose fed rats, GS-834356-induced increased plasma triglycerides were found to be due to increased very-large density lipoprotein (VLDL) secretion and decreased clearance of triglyceride-rich VLDL and chylomicrons[2]. The increase in plasma triglycerides by ACC inhibition was accompanied by an increase in plasma ApoC3 protein, which inhibits lipoprotein lipase activity and suppresses VLDL and chylomicron clearance. ApoC3 transcription in hepatocytes is repressed by the nuclear hormone receptor PPARα[3]. Evaluation of gene transcription profiles of FFD-fed mice treated with the ACC inhibitor GS-834356 revealed a reduction in PPARα target gene signatures[2].These findings suggest that ACC inhibition in the liver leads to a reduction in hepatic PPARα activity and associated increases in VLDL and ApoC3 production, and reduced VLDL/chylomicron clearance. Indeed, the combination of ACC inhibition with PPARα agonism using fenofibrate blocked the ACC-induced plasma TG increases in the mouse NASH model. Importantly, the combination of the ACC inhibitor and fenofibrate caused a similar reduction in hepatic triglycerides compared to ACC inhibitor treatment alone. In addition, the combination caused a greater increase in plasma ketone bodies (a marker of fatty acid beta-oxidation) and a greater reduction of hepatic cholesterol levels relative to ACC inhibition alone[2]. These findings demonstrate that the addition of fenofibrate overcomes triglyceride elevations induced by ACC inhibition and further increases fatty acid oxidation and cholesterol metabolism.

In total, these studies confirm the potential for GS-0976 to impact important metabolic endpoints associated with NASH, and for the addition of PPARα agonists to reverse increases in plasma triglycerides.

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

1.3.3. Nonclinical Toxicology

The nonclinical toxicologic profile of GS-0976 has been well characterized in single- and repeat-dose toxicity studies up to 39 weeks in duration and in genetic toxicity, embryo-fetal developmental toxicity, and local tolerance studies.

GS-0976 was well tolerated up to 13 weeks in the mouse, 26 weeks in the rat, and 39 weeks in the dog. The primary target organ toxicity was the presence of cataracts and/or lens degeneration in the mouse and dog after 2 and 13 weeks, respectively. In the 2-week mouse study, while 1 of 10 female mice at the lowest dose (5 mg/kg/day) had lens degeneration, none of the male mice at the same dose, whereas they did at 3 times higher mean GS-0976 exposure. In the females, the lowest exposure where lens degeneration was observed was 5 times higher than the clinical exposure at 20 mg GS-0976.

In contrast, in the 13-week mouse study, there were no eye findings that were attributed to GS-0976 at exposures approximately 8 fold above the clinical exposure at 20 mg. While the relevance of the lens degeneration observed in the mouse to humans is currently unknown, the lack of eye findings attributable to GS-0976 in the 13-week mouse study and the differences in the eye anatomy between mouse and human suggest that eye findings at lower exposures in the 2-week study may not be clinically relevant. In the dog, lens degeneration/cataracts were first observed after 13 weeks of GS-0976 administration. While lens degeneration/cataracts were also observed in the chronic dog study, these findings occurred at exposures > 168 times the clinical exposure at 20 mg.

There were no adverse eye findings in the chronic dog study at mean exposures at least 48 times the clinical exposure at 20 mg. GS-0976 was not genotoxic and there was no embryo-fetal developmental toxicity at exposures approximately 50 times the clinical exposure. GS-0976 was considered non-corrosive and does not require classification as an eye irritant.

Based on the systemic concentrations of GS-0976 measured in the repeat-dose toxicity studies in mice, rat and dog at the projected clinically efficacious AUC (88 ng•h/mL), the margins of exposure at the NOAELs are 8, 206 and 48 in the mouse, rat and dog, respectively. Thus, data from the nonclinical studies support the continued clinical evaluation of 20 mg GS-0976.

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

1.3.4. 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, NDI-011535, renamed as GS-834773.

Neither GS-0976 nor GS-834773 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 CYP3A4 in human hepatocytes in vitro.

A single nonclinical study to evaluate elimination of GS-0976 and the metabolite GS-834773 was performed in bile duct cannulated Sprague-Dawley rats to profile concentrations over time in plasma, urine, and bile. Overall, the pharmacokinetic (PK) profile in plasma and bile indicate that GS-0976 is rapidly cleared from the plasma compartment, and the primary route of elimination is via the bile.

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

1.3.5. Clinical Trials of GS-0976

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

Information about completed and ongoing clinical studies can be found in the GS-0976 IB, with studies not yet included in the IB briefly described below.

1.3.5.1. Study GS-US-426-4074: A Phase 1 Study to Evaluate Transporter and Cytochrome (CYP) 450-Mediated Drug-Drug Interactions between GS-0976 and Probe Drugs

Study GS-US-426-4074 is an ongoing, open-label, multiple-cohort study designed to evaluate transporter and CYP-mediated drug-drug interactions (DDIs) between GS-0976 (10, 20, or 50 mg) and various probe drugs in healthy subjects. The effect of an organic anion-transporting polypeptide (OATP)1B1/1B3 inhibitor on the PK/PD relationships of GS-0976, as assessed by changes in fractional DNL, will also be evaluated.

1.3.5.1.1. Subject Disposition

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

1.3.5.1.2. Preliminary Safety Results

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

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

1.3.5.1.3. Preliminary PK Results

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

Cohort 1: Impact of OATP/multidrug resistance-associated protein 2 (MRP2)/permeability glycoprotein (P-gp) inhibition (single dose cyclosporine [CsA] 600 mg: CsA) or OATP1B1/1B3 inhibition (single dose rifampin [RIF] 600 mg: RIF) on single dose of GS-0976 20 mg (N=28). Single doses of CsA and RIF significantly increased GS-0976 exposure (21.2- and 18.4-fold, respectively) and resulted in even greater increases in GS-834773 exposures (64.5- and 55.4-fold, respectively). These data indicate GS-0976 is a sensitive substrate of hepatic OATP with intestinal P-gp playing a minimal role in GS-0976 absorption as seen by a smaller increase in GS-0976 C_{max} by CsA compared to single dose RIF.

Cohort 2: Impact of pan-UGT inhibition (probenecid [PBC] 500 mg: PBC) and CYP3A4 inhibition (voriconazole [VORI] 200 mg: VORI) on single dose administration of GS-0976 20 mg (N=14). Co-administration of GS-0976 with PBC resulted in a moderate increase in GS-0976 exposure (61%) indicating UGTs are involved in the metabolism of GS-0976. The moderate increase in GS-834773 exposure (74%) with PBC may be due to inhibition of other enzymes/transporters involved in the clearance of GS-834773. Co-administration of GS-0976 with VORI increased GS-0976 and GS-834773 exposures (37% and 44%, respectively) indicating CYP3A4 plays a small role in the elimination of both parent and metabolite.

Cohort 5: Impact of single and multiple doses of GS-0976 50 mg once daily on a sensitive CYP3A4 probe substrate (midazolam [MDZ] 2 mg: MDZ; N=12). Neither single dose nor multiple doses of GS-0976 altered MDZ exposure (90% CIs of the % geometric mean ration (GMR) for AUC and C_{max} with lack of effect bounds of 70-143%) indicating GS-0976 is not an inhibitor or inducer of CYP3A4.

Cohort 6: Impact of single and multiple doses of GS-0976 50 mg once daily on a representative combined oral contraceptive (drospirenone [DRSP]/EE 3/0.02 mg: DRSP/EE; N=16). There was no effect of single dose GS-0976 on DRSP or EE exposure (90% CIs of the %GMR for AUC and C_{max} with lack of effect bounds of 70-143%). Multiple doses of GS-0976 slightly increased EE exposure (AUC_{inf} increased ~34%) with no effect on DRSP exposure indicating GS-0976 does not induce enzymes/transporters involved in the clearance of DRSP or EE. No loss of contraceptive efficacy is expected upon administration of GS-0976 with oral contraceptives like DRSP/EE. The slight increase in EE exposure is not considered clinically significant and does not warrant dose modification.

Table 1-1. Preliminary Pharmacokinetic Results from Study GS-US-426-4074 Evaluating DDIs with GS-0976 (20 mg or 50 mg)

Inhibitor/Inducer Drug	GS-0976 %GMR (90% CIs)		GS-834773 %GMR (90% CIs)	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
CsA	2120 (1810, 2480)	2000 (1590, 2520)	6450 (5260, 7900)	7870 (6130, 10100)
RIF	1840 (1570, 2150)	2710 (2160, 3400)	5540 (4520, 6790)	10100 (7890, 13000)
PBC	161 (144, 180)	160 (132, 195)	174 (148, 204)	176 (145, 214)
VORI	137 (123, 152)	145 (119, 176)	144 (123, 170)	140 (116, 171)
	MDZ + SD GS-0976 %GMR (90% CIs)		**MDZ + MD GS-0976 %GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
GS-0976 (50 mg)	111 (99.8, 123)	102 (91.6, 115)	102 (91.4, 113)	106 (94.9, 119)
	DRSP + SD GS-0976 %GMR (90% CIs)		**DRSP + MD GS-0976 %GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
GS-0976 (50 mg)	96.4 (86.5, 107)	103 (91.5, 116)	105 (94.0, 117)	116 (102, 131)
	EE + SD GS-0976 %GMR (90% CIs)		**EE + MD GS-0976 %GMR (90% CIs)**	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
GS-0976 (50 mg)	102 (87.6, 119)	112 (104, 122)	134 (114, 156)	121 (111, 131)

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

1.3.5.2. Study GS-US-426-3988: A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of GS-0976 in Subjects with Normal and Impaired Hepatic Function

Study GS-US-426-3988 is an ongoing Phase 1, open-label, parallel-group, single dose study evaluating the safety, tolerability, and PK of GS-0976 in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment (CP class A, B, or C, respectively). Up to 60 subjects are planned for enrollment in 1 of 3 hepatic impairment cohorts: Cohort 1 (mild hepatic impairment), Cohort 2 (moderate hepatic impairment), and Cohort 3 (severe hepatic impairment). Within each cohort, each subject with impaired hepatic function

(N=10 per cohort) will be matched for age (± 10 years), sex, race, and body mass index (BMI): ± 15% with a control subject with normal hepatic function (N=10 per cohort). Data from healthy subjects may be used in >1 cohort if a subject was an appropriate match for a subject with hepatic function in >1 cohort. Subjects in Cohorts 1 and 2 will receive a single oral dose of GS-0976 20 mg in a fasted state on Day 1. Subjects in Cohort 3 will receive a single oral dose of GS-0976 5 mg in a fasted state on Day 1.

1.3.5.2.1. Subject Disposition and Demographics

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

1.3.5.2.2. Preliminary Safety Results

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

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

1.3.5.2.3. Preliminary PK Results

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

- Cohort 1 (Mild Hepatic Impairment; CP A): GS-0976 exposure (AUC_{inf} and C_{max}) was higher in subjects with mild hepatic impairment (approximately 84% and 69%, respectively) as compared to subjects with normal hepatic function. In subjects with mild hepatic impairment, exposure (AUC_{inf} and C_{max}) of the metabolite GS-834773 was also higher (approximately 3.9-fold higher for both). Plasma protein binding of both parent and metabolite were similar in subjects with mild hepatic impairment as compared to subjects with normal hepatic function. GS-0976 is a hepatic OATP substrate and OATP expression/activity may be reduced in patients with cirrhosis. Thus, altered OATP expression/activity may contribute to the observed higher systemic exposure of GS-0976. At a dose of 20 mg once daily in subjects with mild hepatic impairment, exposure margins

relative to preclinical NOAEL exposures for both parent and metabolite are expected to remain adequate.

- Cohort 2 (Moderate Hepatic Impairment; CP B): GS-0976 exposure (AUC_{inf} and C_{max}) was higher in subjects with moderate hepatic impairment (approximately 8.7- and 9.1-fold higher, respectively) as compared to subjects with normal hepatic function. Exposure (AUC_{inf} and C_{max}) of the metabolite GS-834773 was also higher (approximately 37.5- and 44.7-fold higher, respectively). Plasma protein binding of both parent and metabolite were similar in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function. The increased exposure of GS-0976 and GS-834773 in subjects with moderate hepatic impairment is likely due to further decreases in OATP expression/activity relative to mild hepatic impairment as well as decreases in expression/activity of enzymes involved in GS-0976 metabolism (ie, UGTs and CYP3A4). At a dose of 20 mg once daily, GS-0976 plasma exposures in subjects with moderate hepatic impairment are ≥ 5-fold and ≥ 25-fold lower than exposures at the NOAEL in the chronic toxicology studies in dogs and rats, respectively.

Table 1-2. GS-US-426-3988: Preliminary GS-0976 and GS-834773 PK Parameters Following a Single Dose of GS-0976 20 mg in Subjects with Mild or Moderate Hepatic Impairment or Normal Hepatic Function

Cohort	Analyte	Mean (%CV) PK Parameter	Matched Healthy Control (N=10)	Moderate Hepatic Impairment (N=10)	%GMR (90% CI)
1 (Mild HI)	GS-0976	AUC_{inf} (hr ng/mL)	70.4 (55.2)	166 (98.2)	184 (101, 336)
		AUC_{last} (hr ng/mL)	69.6 (55.7)	161 (98.5)	181 (99.3, 331)
		C_{max} (ng/mL)	25.4 (80.6)	50.9 (90.3)	169 (87.5, 325)
	GS-834773	AUC_{inf} (hr ng/mL)	8.29 (69.6)	48.1 (123)	387 (177, 846)
		AUC_{last} (hr ng/mL)	7.38 (79.0)	46.3 (125)	430 (187, 990)
		C_{max} (ng/mL)	2.29 (91.8)	12.9 (125)	391 (164, 935)
2 (Moderate HI)	GS-0976	AUC_{inf} (hr ng/mL)	65.9 (52.3)	687 (72.8)	867 (484, 1550)
		AUC_{last} (hr ng/mL)	64.5 (51.5)	681 (72.9)	879 (491, 1580)
		C_{max} (ng/mL)	20.1 (60.2)	198 (60.0)	905 (539, 1520)
	GS-834773	AUC_{inf} (hr ng/mL)	5.9 (57.5)	399 (135)	3750 (1640, 8560)
		AUC_{last} (hr ng/mL)	5.1 (62.9)	396 (136)	4410 (1900, 10200)
		C_{max} (ng/mL)	1.4 (81.2)	77.3 (72.5)	4470 (2190, 9130)

Data presented to 3 significant figures

Based on the preliminary PK data from this study as well as the overall safety profile of GS-0976, dose adjustments are not considered necessary in subjects with mild hepatic impairment.

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

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

The primary endpoint was the safety of GS-0976. CCI

[redacted]

1.3.5.3.1. Subject Disposition

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

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

1.3.5.3.2. Safety Results

Treatment with GS-0976 20 or 5 mg was generally well tolerated. The most common AEs in each treatment group were nausea, abdominal pain, and diarrhea (GS-0976 20 mg); diarrhea, headache, and hypertriglyceridemia (GS-0976 5 mg); and fatigue, sinusitis, nausea, chest discomfort, constipation, and dyspnea (placebo). Most AEs were Grade 1 or 2 in severity. Overall, 5 subjects had a Grade 3 AE. These AEs included abdominal pain, back pain, HE, hyperglycemia, hypertriglyceridemia, sepsis, transient ischemic attack, and diverticulitis. None of the Grade 3 AEs were reported in > 1 subject, and all but 1 was considered unrelated to study drug. One Grade 4 AE, which was not considered treatment-related, was reported. SAEs were reported for 4 subjects and included transient ischemic attack, sepsis, pyrexia, abdominal pain,

HE, and diverticulitis. There were no trends in SAE type or time of onset, no SAE was reported in > 1 subject, and all SAEs were considered unrelated to study drug. Two subjects had AEs leading to premature discontinuation of study drug; for 1 of these subjects, the AEs leading to study drug discontinuation (pruritus, rash papular, and night sweats) were considered treatment-related. No deaths occurred during the study.

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

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

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

1.3.5.3.3. Efficacy Results

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

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

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

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

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

- Hyaluronic acid (HA): −6.9% (−22.2%, 35.0%) in the GS-0976 20 mg group, −0.7% (−29.0%, 30.3%) in the GS-0976 5 mg group, and −15.3% (−25.4%, 20.9%) in the placebo group

- Tissue inhibitor of metalloproteinase 1 (TIMP1): −7.9% (−17.2%, 0.1%) in the GS-0976 20 mg group, −2.9% (−13.9%, 5.8%) in the GS-0976 5 mg group, and 1.5% (−9.0%, 10.6%) in the placebo group

- Procollagen III amino terminal peptide (PIIINP): −13.9% (−23.6%, 9.4%) in the GS-0976 20 mg group, −7.0% (−15.3%, 10.9%) in the GS-0976 5 mg group, and −0.5% (−7.9%, 4.3%) in the placebo group.

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

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

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

1.4. General Information for GS-9674

1.4.1. GS-9674

GS-9674 is a potent and selective agonist of the Farnesoid X Receptor (FXR) whose activity in intestinal epithelial cells results in the release of fibroblast growth factor 19 (FGF19). FGF19 is an endocrine peptide which drives a signaling cascade to decrease lipogenesis, gluconeogenesis, hepatic triglyceride accumulation, and bile acid synthesis. Thus GS-9674, by agonizing FXR, is expected to improve NASH. Please refer to the Investigator's Brochure (IB) for additional information on GS-9674, including:

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

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

In vivo pharmacology studies have demonstrated that GS-9674 preferentially activates intestinal FXR and reduces liver fibrosis. In cynomolgus monkeys, there was an increase in circulating FGF19 levels after oral dosing of GS-9674 but not after IV dosing despite greater exposure to GS-9674 after IV dosing. These data suggest that intestinal FXR agonism by GS-9674 causes FGF19 production, whereas low systemic free drug concentrations limit effects following IV administration of GS-9674. In addition, the oral administration of GS-9674 to monkeys directly activated intestinal FXR, as measured by the expression of FXR-target genes in the ileum (FGF19, OSTα, and OSTβ mRNA). In a mouse model of NASH induced by a diet enriched in fat, cholesterol and sugar, GS-9674 reduced hepatic steatosis and normalized bile acid levels in plasma. In a choline-deficient high fat diet /NaNO2 rat model of liver fibrosis that utilizes "2 hits" to mimic the metabolic and oxidative stress components of NASH in humans, GS-9674 dose dependently reduced both biochemical and histological measures of liver fibrosis. Overall, the results from these pharmacology studies demonstrate that GS-9674 is a potent and selective agonist of intestinal FXR with the potential to benefit NASH patients by inducing FGF19 production.

GS-9674 has low oral bioavailability, volume of distribution and clearance with very high plasma protein binding (>99.6%) across species. Elimination of GS-9674 is primarily through the fecal route. GS-9674 undergoes oxidative metabolism in human hepatocytes via CYP2C8, CYP3A4, and CYP2C19. Potent inhibitors of these CYPs therefore may affect metabolism of GS-9674. GS-9674 had little inhibitory effect on the activities of CYP1A2, CYP2B6, CYP2C19 or CYP2D6. Whereas CYP2C8, CYP2C9, and CYP3A were moderately inhibited, GS-9674 was not a mechanism-based inhibitor of these enzymes. GS-9674 showed moderate inhibition of human UGT1A1, sodium-taurocholate cotransporting polypeptide (NTCP), and bile salt export

pump (BSEP) and strongly inhibited human OATP1B1, OATP1B3, and OATP2B1. GS-9674 has the potential to affect hepatic/intestinal uptake of OATP substrates or metabolism of CYP2C8, CYP2C9, or CYP3A4 substrates. However, low solubility, high protein binding and low systemic levels may reduce the potential for GS-9674 to cause drug-drug interactions at clinically relevant exposures via inhibition of metabolic enzymes and transporters. GS-9674 is a substrate for efflux transporters P-glycoprotein and breast cancer resistance protein (BCRP), as well as the hepatic uptake transporters OATP1B1, 1B3, and 2B1, and NTCP. Inhibitors or genetic polymorphisms affecting the activity of these transporters may affect GS-9674 intestinal absorption and hepatic uptake.

Based on nonclinical assays, GS-1056756 (the R-enantiomer of M13), an inactive, major circulating metabolite of GS-9674 has shown low potential to inhibit CYP enzymes (IC_{50} values of 3.49 for CYP2C8 and >25 uM for CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6) and UGT (IC_{50} value of 13.9 for UGT1A1) in vivo. GS-1056756 did not inhibit P-gp, BCRP, OCT2, MATE1, MATE2K, and showed low probability to be clinically relevant inhibitor of OAT1, OCT1, OATP1B1, OATP1B3 or OATP2B1. No clinical DDI liability of GS-1056756 on enzymes and transporters was predicted from in vitro characterizations.

GS-1056756 has been identified in nonclinical assays as a substrate of OATP1B1/1B3. In vitro, GS-1056756 is formed by oxidative metabolism by CYP3A4 and CYP2C8 with additional conversion to enantiomers by dehydrogenases (eg, ALDH), and is subsequently metabolized by CYP3A and CYP2C8 and UGTs. Together with available clinical data described in Section 1.4.3, the potential clinical DDI liability of GS-1056756 is low.

The nonclinical toxicity profile of GS-9674 has been assessed in mice and cynomolgus monkeys administered GS-9674 orally for up to 26 and 39 weeks, respectively. Findings attributed to GS-9674 administration were primarily related to the liver (increases in alkaline phosphatase, decreases in serum bile acids, cholesterol and triglycerides, increases in liver weight and hepatocellular hypertrophy) and were likely related to the pharmacology of GS-9674. These findings were minimal to mild, non-adverse, and reversible after discontinuation of treatment. The NOAELs after 26 and 39 weeks of dosing in mice and monkeys, respectively, were associated with exposures (AUC_{24h}) that were 22- and 32-fold higher in mice and monkeys, respectively, than the observed exposure in humans administered 100 mg GS-9674 once daily with food.

Refer to the GS-9674 IB for additional details.

1.4.3. Clinical Trials of GS-9674

As of 07 January 2019, 4 Phase 1 and 1 Phase 2 clinical studies have been completed and 8 Phase 1 or 2 studies are ongoing Approximately 1161 subjects have been dosed with GS-9674: approximately 462 subjects in Phase 1 studies, approximately 577 subjects in Phase 2 NASH studies, 70 subjects in 1 Phase 2 PBC study, and 52 subjects in 1 Phase 2 PSC study.

Information about ongoing and completed clinical studies can be found in the current GS-9674 IB, with studies not yet included in the IB briefly described below.

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

Study GS-US-402-3885 is an ongoing Phase 1, open-label, parallel-group, single dose study evaluating the safety, tolerability, PK, and PD of GS-9674 in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment. Up to 60 subjects are planned for enrollment in 1 of 3 hepatic impairment cohorts: Cohort 1 (mild hepatic impairment, CP A), Cohort 2 (moderate hepatic impairment, CP B), and Cohort 3 (severe hepatic impairment, CP C). Within each cohort, each subject with impaired hepatic function (N=10 per cohort) will be matched for age (± 10 years), sex, race, and body mass index (BMI: ± 15%) with a control subject with normal hepatic function (N=10 per cohort). Data from healthy subjects may be used in >1 cohort if a subject was an appropriate match for a subject with hepatic function in >1 cohort. All subjects will receive a single oral dose of GS-9674 30 mg in the fed state on Day 1 with PD collected on Day -1 and Day 1.

A brief summary of preliminary results that are not included in the IB from ongoing study GS-US-402-3885 is presented below. Preliminary clinical PK data for the newly identified major circulating GS-9674 metabolite GS-1056756 (the R-enantiomer of M13) is described in Section 1.4.3.1.3. Briefly, GS-1056756 exhibits a plasma half-life of approximately 175 h. Preliminary steady-state plasma concentrations of GS-1056756 in PSC patients administered 100 mg GS-9674 are as expected based on the preliminary single dose PK data for GS-1056756 from the ADME study (GS-US-402-4287). Additionally, plasma exposures of GS-1056756 are minimally altered in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. These data, taken together with the adequate safety margins from nonclinical safety studies and the nonclinical understanding of the metabolic formation (CYP3A and CYP2C8) and clearance (CYP3A, CYP2C8, and UGTs) mechanisms of GS-1056756 support the concomitant medication restrictions in Section 5.8.

1.4.3.1.1. Subject Disposition

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

1.4.3.1.2. Preliminary Safety Results

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

In the mild hepatic impairment cohort, there were 2 subjects (20%) that had Grade 3 lab abnormalities of elevated GGT and low platelets. The Grade 3 GGT was stable from the subject's baseline. There was 1 healthy matched control subject (10%) who had Grade 3 lab

abnormalities in total cholesterol and LDL cholesterol, which were stable from their baseline. In the moderate hepatic impairment cohort, 2 subjects (20%) had Grade 3 lab abnormalities. One subject had low lymphocytes, and the other subject had elevated total bilirubin and low platelets. The platelet count was not changed from the subject's baseline. One subject, who had a SAE of gastrointestinal bleeding in the moderate hepatic impairment cohort (described above), had a Grade 4 lab abnormality of low hemoglobin.

1.4.3.1.3. Preliminary PK Results

Preliminary PK results are presented below and in Table 1-4:

- Cohort 1 (mild hepatic impairment; CP A): GS-9674 exposure (AUC_{inf} and C_{max}) was higher in subjects with mild hepatic impairment (approximately 76% and 57%, respectively) as compared to subjects with normal hepatic function. In subjects with mild hepatic impairment, exposure (AUC_{inf} and C_{max}) of the metabolite GS-716070 was similarly higher (approximately 64% and 25%, respectively). Overall exposure for GS-1056756 was modestly higher (AUC_{inf} was increased 28% and C_{max} increased 7%) in subjects with mild hepatic impairment compared with subjects with normal hepatic function. GS-9674 and GS-716070 had minor changes in plasma protein binding (unbound fraction [f_u] increased ~30%). GS-9674 is a hepatic OATP substrate and OATP expression/activity may be altered in patients with cirrhosis. Thus, altered OATP expression/activity may contribute to the observed higher systemic exposure of GS-9674. At a dose of 100 mg once daily in subjects with mild hepatic impairment, exposure margins relative to preclinical NOAEL exposures for both parent and metabolites are expected to remain adequate.

- Cohort 2 (moderate hepatic impairment; CP B): GS-9674 exposure (AUC_{inf} and C_{max}) was higher in subjects with moderate hepatic impairment (approximately 2.3- and 1.6-fold, respectively) as compared to subjects with normal hepatic function. Exposure (AUC_{inf}) of the metabolite GS-716070 was also higher (approximately 1.6-fold) with minimal change in C_{max}. GS-1056756 AUC_{inf} was increased 16% and C_{max} was 30% lower in subjects with moderate hepatic impairment compared with subjects with normal hepatic function. Plasma unbound fraction (f_u) of GS-9674 and GS-716070 was increased ~96% and ~85%, respectively, in moderate hepatic impairment, leading to a > 4-fold and > 3-fold increase in free drug exposures of parent and metabolite, respectively.

- Cohort 3 (severe hepatic impairment; CP C): GS-9674 exposure (AUC_{inf} and C_{max}) was higher in subjects with severe hepatic impairment (approximately 6.2- and 2.5-fold, respectively) as compared to subjects with normal hepatic function. Exposure (AUC_{inf}) of the metabolite GS-716070 was also higher (approximately 3-fold) with C_{max} reduced by 33%. GS-1056756 AUC_{inf} was approximately 2.6-fold higher and C_{max} approximately 39% lower in subjects with severe hepatic impairment compared with subjects with normal hepatic function.

Table 1-3. GS-US-402-3885: Preliminary GS-9674, GS-716070, and GS-1056756 PK Parameters Following a Single Dose of GS-9674 30 mg or 10 mg in Subjects with Hepatic Impairment or Normal Hepatic Function

Cohort	Analyte	Mean (%CV) PK Parameter	Matched Healthy Control (N=10)	Hepatic Impairment (N=10)	%GMR (90% CI)
1 (Mild HI, GS-9674 30 mg)	GS-9674	AUC_{inf} (hr ng/mL)	3030 (40.5)	5410 (40.2)	176 (127, 253)
		AUC_{last} (hr ng/mL)	2970 (41.4)	5380 (40.4)	178 (128, 247)
		C_{max} (ng/mL)	604 (45.6)	994 (53.7)	157 (108, 229)
	GS-716070	AUC_{inf} (hr ng/mL)	1440 (49.7)	2330 (44.8)	164 (104, 259)
		AUC_{last} (hr ng/mL)	1400 (51.1)	2300 (44.8)	169 (115, 247)
		C_{max} (ng/mL)	179 (42.6)	234 (50.8)	125 (85.0, 188)
	GS-1056756	AUC_{inf} (hr ng/mL)	2040 (57.7)	2850 (69.5)	128 (80.1, 204)
		AUC_{last} (hr ng/mL)	850 (45.6)	1030 (70.0)	109 (73.0, 163)
		C_{max} (ng/mL)	13.0 (44.4)	15.5 (70.1)	107 (70.4, 161)
2 (Moderate HI, GS-9674 30 mg)	GS-9674	AUC_{inf} (hr ng/mL)	2810 (30.3)	8280 (91.4)	230 (163, 324)
		AUC_{last} (hr ng/mL)	2460 (30.9)	8220 (91.1)	249 (169, 367)
		C_{max} (ng/mL)	496 (40.2)	909 (52.5)	164 (115, 233)
	GS-716070	AUC_{inf} (hr ng/mL)	1380 (47.7)	3160 (81.8)	163 (95.1, 280)
		AUC_{last} (hr ng/mL)	1340 (48.8)	3090 (80.9)	197 (117, 329)
		C_{max} (ng/mL)	168 (51.6)	181 (61.5)	89.5 (54.3, 147)
	GS-1056756	AUC_{inf} (hr ng/mL)	1620 (41.6)	1900 (41.2)	116 (83.5, 161)
		AUC_{last} (hr ng/mL)	734 (40.7)	586 (34.0)	79.4 (58.3, 108)
		C_{max} (ng/mL)	11.6 (39.7)	8.25 (37.6)	70.0 (50.2, 97.6)

Cohort	Analyte	Mean (%CV) PK Parameter	Matched Healthy Control (N=10)	Hepatic Impairment (N=10)	%GMR (90% CI)
3 (Severe HI, GS-9674 10 mg)	GS-9674	AUC_{inf} (hr ng/mL)	989 (36.4)	6710 (60.3)	623 (430, 905)
		AUC_{last} (hr ng/mL)	963 (37.2)	6535 (58.0)	631 (437, 913)
		C_{max} (ng/mL)	182 (47.5)	427 (32.0)	254 (177, 365)
	GS-716070	AUC_{inf} (hr ng/mL)	2450 (77.5)	688 (50.1)	303 (173, 528)
		AUC_{last} (hr ng/mL)	2070 (71.2)	653 (52.9)	280 (166, 473)
		C_{max} (ng/mL)	47.9 (45.6)	77.2 (55.7)	67.0 (44.3, 101)
	GS-1056756	AUC_{inf} (hr ng/mL)	520 (38.8)	3360 (181)	262 (118, 581)
		AUC_{last} (hr ng/mL)	241 (39.2)	181 (45.8)	73 (51.0, 104)
		C_{max} (ng/mL)	3.67 (37.0)	2.35 (50.2)	60.7 (41.9, 88.0)

Data reported to 3 significant figures

- Preliminary PD results for Cohort 1 are also available for change from baseline (Day -1) in plasma FGF19 and serum 7-alpha-hydroxy-4-cholesten-3-one (C4) levels following a single 30-mg dose of GS-9674. Changes in FGF19 and C4 following a single dose of GS-9674 were similar in the mild hepatic impairment subjects as compared to the healthy matched controls as indicated by the PD parameter ratios (mild hepatic impairment/healthy) for C_{max} and $AUC_{2\text{-}12hr}$ for FGF19 (1.1 and 1.1, respectively) and for C_{min} and $AUC_{2\text{-}12hr}$ for C4 (0.82 and 0.87, respectively) that were not significantly different from 1.

- Based on the preliminary PK and PD data from this study as well as the overall safety profile of GS-9674, dose adjustments are not considered necessary in subjects with mild hepatic impairment.

For further information on GS-9674, refer to the current IB.

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

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

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

In support of this hypothesis, pairwise combinations of an ASK1 inhibitor, an FXR agonist, and an ACC inhibitor were well tolerated and caused a greater reduction in fibrosis compared to the respective single agents in a rat choline-deficient, high-fat diet (CDHFD) model of fibrosis. Rats were fed a CDHFD for 6 weeks to induce severe lipotoxicity in the liver and moderate fibrosis. The animals were then maintained on the CDHFD for another 6 weeks while being treated therapeutically with a vehicle control, ASK1 inhibitor, FXR agonist, ACC inhibitor or pairwise combinations of each drug. Fibrosis was assessed histologically by staining extracellular matrix with picrosirius red (PSR). Additionally, the number of activated hepatic stellate cells was quantified by staining liver sections with antibodies against α–SMA and desmin. Quantitative morphometry was performed to determine the percent positive area for each marker. Treatment with the ASK1 inhibitor monotherapy or FXR agonist monotherapy led to small and nonsignificant reductions in PSR area whereas the ACC inhibitor monotherapy led to a significant reduction in PSR area of about 50% relative to vehicle control animals. The FXR and ASK1 combination significantly decreased PSR area by 69% relative to vehicle control animals, which was significantly greater efficacy than that for each respective single agent. Combinations of the ACC inhibitor with either the ASK1 inhibitor or the FXR agonist trended towards greater reduction in PSR % area than the ACC inhibitor alone, each reaching 60% reduction. All pairwise combinations significantly reduced α-SMA and desmin area to a greater extent than the single agents alone. In addition, all pairwise combinations led to greater reductions in plasma markers of fibrosis TIMP1 and PIIINP compared to each respective single agent. These data demonstrate that pairwise combinations of each of the agents increased anti-fibrotic efficacy assessed by multiple different markers. Therefore, combinations of SEL, GS-9674 and GS-0976 have the potential to induce a greater magnitude of fibrosis reversal in subjects with NASH.

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

Pharmacodynamic analysis for ASK1, FXR and ACC signaling confirmed that these targets regulate independent pathways that contribute to NASH pathogenesis. Treatment of mice with an ASK1 inhibitor did not agonize the FXR pathway or inhibit the ACC pathway. Similarly, treatment of mice with an FXR agonist did not impinge on the ASK1 or ACC pathways and the ACC inhibitor did not agonize the FXR pathway or inhibit the ASK1 pathway. Therefore, each agent is expected to cause a therapeutic benefit independent of the other monotherapies. These data suggest that a triple combination therapy of SEL, GS-0976 and GS-9674 may be even more efficacious to reverse fibrosis than double combination therapies.

In a 13-week repeat dose combination toxicity monkey study, SEL and GS-9674 when administered separately or in combination resulted in no adverse findings.

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

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

GS-0976 was also administered in combination with SEL to rats for 13 consecutive weeks. Microscopic findings of hyperkeratosis and hyperplasia, edema, ulceration, erosion, and/or focal squamous epithelial degeneration of the non-glandular stomach were observed at 30 mg/kg/day GS-0976, and in all combination groups. The non-glandular stomach findings occurred in a dose-dependent manner were considered adverse in the 5/10 and 15/30 mg/kg/day SEL/GS-0976 groups. However, the findings do not have any relevance to humans since humans do not have a non-glandular stomach. In the lung, aggregates of macrophages, with or without interstitial mononuclear infiltrates and cholesterol clefts, were noted in all groups, including the vehicle control group. While this finding was considered adverse in the high dose combination group due to increased incidence and severity, an increased occurrence after gavage dosing can also be indicative of mechanically induced reflux. The NOAEL for this study that is relevant to human safety is the 5/10 mg/kg/day SEL/GS-0976 group with corresponding SEL/GS-0976 exposure margins of 1/6 times above the clinical exposures.

There were no new or additive toxicities observed in the dual combination toxicity studies that would be considered relevant to human. The triple combination of SEL, GS-0976 and GS-9674 is not expected to change the current toxicity profile of the individual agents. Thus, the nonclinical safety data support the clinical evaluation of the triple combination.

1.5.2. Clinical Trials

1.5.2.1. GS-US-402-2101

Study GS-US-402-2101 is a Phase 1, open-label, multiple-cohort, multiple-dose study designed to evaluate potential drug-drug interactions between SEL 18 mg, GS-9674 100 mg, and GS-0976 20 mg in healthy subjects (Cohorts 3-5). Study conduct is complete. Cohorts 1 and 2, designed to evaluate potential combination DDIs using a lower dose of GS-9674, and Cohort 6, designed to

evaluate the potential DDIs between all three agents, were not conducted based on preliminary data from Cohorts 3 through 5. A total of 108 subjects were enrolled in Cohorts 3 through 5.

1.5.2.1.1. Subject Disposition and Demographics

As of 18 January 2017, a total of 108 subjects were enrolled; 104 subjects had completed study treatment. 4 subject prematurely discontinued study treatment, with 1 subject prematurely discontinuing due to an AE. 2 subjects withdrew consent and 1 subject was lost to follow-up.

1.5.2.1.2. Safety Results

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

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

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

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

1.5.2.1.3. Summary of PK Results

The changes in the primary PK parameters for SEL, GS-9674, and GS-0976 and their respective metabolites (GS-607509, GS-716070, and GS-834773) following once-daily administration of SEL, GS-9674, and/or GS-0976 in combination for 7 days compared with the single agent for

7 days are summarized in the Table 1-4. None of modest changes observed were considered clinically significant, and no dose modifications were needed upon coadministration of SEL, GS-9674, and/or GS-0976.

Table 1-4. GS-US-402-2101: Changes in primary PK parameters for SEL, GS-9674, and GS-0976 and their respective metabolites (GS-607509, GS-716070, and GS-834773) following once daily administration of SEL, GS-9674, and/or GS-0976 in combination for 7 days compared with the single agent for 7 days

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

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

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

GS-0976 and GS-834773 exposures following 20 mg once-daily dosing of the tablet formulation under fasting conditions (Cohort 3) were similar to those previously observed following 20 mg once-daily dosing of the capsule formulation under fasting conditions (Study GS-US-426-3987).

1.5.2.2. GS-US-384-3914

Study GS-US-384-3914 is an ongoing proof of concept, open-label, multiple-cohort study designed to evaluate the safety and efficacy of SEL, GS-0976, and GS-9674 alone and in combination in subjects with NASH and stage 2 to 3 fibrosis (by NASHCRN criteria) as evaluated by a MRE ≥ 2.88 kPa and an MRI-PDFF ≥ 10% or a historical biopsy within 12 months of Screening. Cohorts 1 through 3 are monotherapy cohorts, and Cohorts 4 through 6 are combination cohorts. All Cohorts were designed to receive study drug for 12 weeks duration Preliminary results from Cohorts 1-3 and 4-6 are provided below.

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

As of September 29, 2017, a total of 30 were enrolled (n=10 for each Cohort) and all had completed study treatment. There were no subjects who prematurely discontinued study drug. No subjects withdrew consent, and no subjects were lost to follow-up.

1.5.2.2.2. Preliminary Safety Results

Overall, 50% (5/10) of subjects had a TEAE in each of Cohorts 1 and 3, and 60% (6/10) of subjects had TEAE in Cohort 2. There were no Grade 3 or 4 adverse events, and no serious adverse events. In Cohort 1 and Cohort 2, the most common adverse events occurred in the system organ class of GI disorders, with 20% (2/10) of subjects in each Cohort experiencing this type of adverse event. In Cohort 3, the system organ class of infections and infestations included the most common adverse events at 40% (4/10).

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

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

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

1.5.2.2.4. Preliminary Safety Results

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

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

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

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

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

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

1.5.2.2.6. Preliminary Safety Results

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

In Cohort 7, 4 subjects (40%) experienced Grade 3 laboratory abnormalities. One subject had a transient decrease in their neutrophils. Two subjects had hyperglycemia, and one of these hyperglycemia subjects had concurrent Grade 3 hyponatremia that resolved with improved glycemic control. One subject had asymptomatic hypertriglyceridemia that resolved with fibrate treatment. In Cohort 8, 3 subjects (30%) had Grade 3 lab abnormalities. One subject had a transient hypophosphatemia and one subject had hyperglycemia. One subject had an increase in

their INR on Day 84 that was believed to be a lab error and normalized on repeat testing without intervention. Also, there were no concurrent changes in liver biochemistry testing with this transient increase in INR.

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

Table 1-5. GS-US-384-3914: Safety Summary

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

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

Table 1-6. GS-US-384-3914: Treatment-Emergent Grade 3 and 4 Lab Abnormality Summary

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

1.6. Information about Fenofibrate

Fenofibrate is a pro-drug of the active chemical moiety fenofibric acid which is a PPARα activator. Fenofibrate is indicated as an adjunct to diet to reduce elevated LDL-C, Total-C, triglyceride and ApoB, and to increase HDL-C in adult patients with primary hypercholesterolemia and for treatment of adult patients with severe hypertriglyceridemia. Fenofibrate is available as 48 or 145 mg tablets for once daily oral administration without regard to meals. For treatment of severe hypertriglyceridemia the recommended initial dose of fenofibrate is 48 to 145 mg once daily and should be individualized according to patient response and adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals with the maximum dose of 145 mg daily. In patients with mild to moderately impaired renal function fenofibrate should be initiated at a dose of 48 mg once daily and increased only after evaluation of the effects on renal function and lipid levels at this dose. The use of fenofibrate has not been evaluated in formal hepatic impairment studies; as such fenofibrate usage is contraindicated in subjects with active liver disease. However, use of fibrates (including fenofibrate) has been described in subjects with liver disease, including those with cirrhosis, due to primary biliary cholangitis. In these studies, the safety of fibrate therapy has been consistent with data in subjects without pre-existing liver disease {Corpechot 2018}. Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate (>2% and at least 1% greater than placebo). The risk for myopathy and rhabdomyolysis are increased when fibrates are co-administered with a statin, particularly in elderly patients and patients with diabetes, renal failure, or hypothyroidism.

Fenofibrate can increase serum transaminases and reversibly increase serum creatinine (>2% and at least 1% greater than placebo). Liver tests including ALT should be monitored periodically during therapy. Renal function should be monitored periodically in patients with renal impairment. Fenofibrate increases cholesterol excretion into the bile, which may lead to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Concomitant oral coumarin anticoagulants should be used with caution with fenofibrate. Dose of coumarin anticoagulants should be adjusted to maintain prothrombin time/INR at the desired level to prevent bleeding complications.

1.7. Information about Vascepa®

Vascepa® (Icosapent ethyl) contains ethyl esters of an omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from fish oil. It contains ≥96% EPA and does not contain docosahexaenoic acid (DHA). Historically, mixtures containing both EPA and DHA have increased LDL cholesterol in patients with severe hypertriglyceridemia. However, studies have suggested that icosapent ethyl has not caused significant increases in LDL cholesterol while significantly decreasing triglyceride levels. In a placebo-controlled, double-blind clinical trial that enrolled patients with high fasting triglyceride levels (135 to 499 mg/dL) and established cardiovascular disease or diabetes and other risk factors, it was found that patients who received 2 grams of Vascepa® twice daily had significantly lower risk of ischemic events compared to placebo{Bhatt 2019}.

1.8. Rationale for This Study

NASH involves as complex interplay between hepatocytes, immune cells, and hepatic stellate cells that perpetuates a pathological cycle of hepatocyte injury, inflammation and fibrosis {Caligiuri 2016}. Increased synthesis and accumulation of fatty acids in hepatocytes leads to lipotoxicity, a state characterized by increased production of toxic lipid metabolites, bile acids, reactive oxygen species, growth factors, and ultimately hepatocyte cell death {Neuschwander-Tetri 2010}. These metabolic stress signals directly promote the activation and differentiation of hepatic stellate cells into myofibroblasts, the primary source of collagen and extracellular matrix that causes fibrosis. In addition, hepatocyte lipotoxicity promotes an immune response by resident macrophages, which produce ROS, growth factors and cytokines such as transforming growth factor beta (TGFβ) and platelet-derived growth factor (PDGF), that further increase myofibroblast activation, migration, proliferation and survival and fibrosis {Lee 2015}. Based on the multiple biological pathways involved in the pathogenesis of NASH, and the heterogeneity of the patient population, it is likely that a combination of drugs that have distinct mechanisms of action will be needed to achieve optimal therapeutic benefit. ASK1 inhibition with SEL reduces oxidative stress-induced hepatocyte apoptosis, inflammation and fibrogenesis by reducing activation of JNK and p38 stress-response kinases. Thus, SEL is postulated to halt several instigating triggers for NASH. ASK1 inhibition reduces hepatic steatosis and fibrosis in obese mice fed a fat and carbohydrate rich diet, and reduces liver fibrosis in rats fed a choline-deficient, high-fat diet. In a recently-completed Phase 2 study in subjects with NASH (GS-US-384-1497), SEL dose-dependently reduced liver fibrosis, demonstrating that ASK1 inhibition causes regression of liver fibrosis in humans. Increased rates of hepatic DNL and insufficient fatty acid oxidation lead to hepatic steatosis and associated lipotoxicity, which are also implicated in the

etiology and progression of NASH. By inhibiting ACC, GS-0976 has been shown to reduce steatosis and fibrosis in animal models of NASH and to reduce DNL by >70% at doses of 20 mg daily in humans. Reduction of DNL by GS-0976 is therefore expected to improve steatosis and fibrosis in subjects with NASH. FXR agonism has been shown to reduce hepatic lipid and bile acid synthesis due to down regulation of SREBP-1c and CYP7A1, respectively, as well as reduce insulin resistance and hepatic gluconeogenesis {Zhang 2006}. Thus, GS-9674 is postulated to halt these instigating triggers for NASH {Zhang 2006}. Animal models have demonstrated the ability of GS-9674 to reduce hepatic fibrosis in a choline-deficient high fat diet /$NaNO_2$ rat model of NASH and to reduce hepatic steatosis in obese mice fed a fat and carbohydrate rich diet. Preclinical studies in animal models of NASH have demonstrated that combinations of an ASK1 inhibitor and ACC inhibitor, ASK1 inhibitor and FXR agonist, and FXR agonist and ACC inhibitor lead to greater efficacy to reduce hepatic steatosis and measures of liver fibrosis compared to the respective monotherapies. Triple combination therapy of SEL, GS-9674 and GS-0976 has potential to further increase efficacy by targeting three distinct pathways that independently contribute to NASH pathogenesis. Combination toxicology studies have revealed no new toxicities of SEL and GS-9674, SEL and GS-0976, or GS-9674 and GS-0976.

NASH with fibrosis is a condition with a high risk of progression to cirrhosis which may lead to end-stage liver disease and increases the risk of hepatocellular carcinoma. Thus, reversing the fibrotic process in addition to ameliorating the metabolic dysfunction that drives NASH pathogenesis is paramount to improving the prognosis of this condition. The current gold standard for assessing fibrosis – liver biopsy – is invasive, prone to complications, and is not appropriate for use as an endpoint in a study of 12 weeks duration. As such, this study will incorporate noninvasive endpoints for the assessment of fibrosis including serum markers (eg, ELF™ test), imaging (eg, MRE), and deuterated water labeling. Deuterated water labeling allows for a rate-based assessment of disease activity including fibrogenesis {Decaris 2015} and also evaluation of changes in the rate of other metabolic processes relevant to NASH (eg, DNL, cytokine production, etc.) {Allister 2015}.

Previous clinical studies with GS-0976 20 mg have demonstrated that some patients experience hypertriglyceridemia with ACC inhibition. In the Phase 2 study (GS-US-426-3989, Section 1.3.5.3) described above, 7 out of 49 subjects (14%) with F1 to F3 fibrosis due to NASH experienced asymptomatic, treatment-emergent Grade 3-4 hypertriglyceridemia (>500 mg/dL) while being treated with GS-0976 20 mg daily for 12 weeks. In study GS-US-426-3989, the median relative increase from baseline in serum triglycerides was 11% in GS-0976 20 mg treated subjects. In this study, GS-US-384-3914 (Section 1.5.2.2), subjects with F2 to F4 fibrosis due to NASH have been treated with GS-0976 20 mg alone and in combination with other compounds. In each of these GS-0976-containing Cohorts described above (Cohorts 2, 5, 6, and 7) 10% of subjects have experienced asymptomatic, treatment-emergent Grade 3-4 hypertriglyceridemia.

Preclinical studies described above (Section 1.3.2) suggest there are two mechanisms contributing to hypertriglyceridemia with ACC inhibition: 1) increased production and secretion of TG-rich VLDL particles from the liver and 2) decreased clearance of TG-rich lipoproteins (i.e. chylomicrons and VLDL particles) from the circulation. Data from these preclinical models

of NASH suggest that transrepression of PPAR-α and subsequent inhibition of lipoprotein lipase (LPL) through an increase in ApoC3 both contribute to the hypertriglyceridemia.

In the Phase 2 study (GS-US-426-3989) and in this study (GS-US-384-3914), all 13 of the subjects with Grade 3-4 hypertriglyceridemia had elevated triglycerides (>150 mg/dL) at baseline. In the Phase 2 study, the most important predictor of Grade 3-4 treatment-emergent hypertriglyceridemia was the presence of triglycerides >250 mg/dL. Whereas treatment-emergent triglycerides >500 mg/dL were observed in 17% of subjects with baseline triglycerides between 150 and 250 mg/dL, 43% of patients with baseline triglycerides >250 mg/dL developed Grade-3-4 hypertriglyceridemia.

In studies including GS-0976 20 mg, a subset of patients with Grade 3-4 hypertriglyceridemia were treated with PPAR-α agonists (e.g. fibrates or fish oil), and all these patients had reductions in their triglycerides towards their baseline levels without any discontinuations in GS-0976 treatment. In GS-US-426-3989, 1 subject was treated with fenofibrate for Grade 3 hypertriglyceridemia; and this subject was noted to have decrease in the triglycerides, ApoB48, VLDL particles, and ApoC3 to their baseline levels despite continued treatment with GS-0976 20 mg were noted.

In previous studies, there are a total of 11 patients who have received GS-0976 20 mg and were already receiving a PPAR-α medication (3/11 on a fibrate, 8/11 on fish oil) prior to starting GS-0976. These patients had a median decrease in their triglycerides of -0.9 mg/dL, and none of these subjects experienced treatment-emergent Grade 3-4 hypertriglyceridemia. This subset of patients also demonstrated greater improvements in liver biochemistry, serum markers of fibrosis, imaging parameters for hepatic steatosis and fibrosis (MRI-PDFF, MRE, and FibroScan®) compared to subjects treated with GS-0976 20 mg without a PPAR-α agonist. This preliminary data suggests the combination of GS-0976 and PPARα agonists are safe and that there may be a synergistic benefit in terms of increased beta-oxidation and treatment for NASH with ACC inhibition from GS-0976 and a PPAR-α agonist, as indicated in the preclinical studies described previously.

Among subjects with baseline hypertriglyceridemia (serum triglycerides ≥ 150 mg/dL and < 500 mg/dL), data from study GS-US-384-3914 Cohorts 2, 5, 6, and 7, which treated subjects with either GS-0976 (20 mg), or GS-0976 (20 mg) + GS-9674 (30 mg), as well as data from study GS-US-426-3989 Treatment Group B, which treated subjects with GS-0976 (20 mg), showed a mean increase in triglycerides of 80 mg/dL from baseline at 4 weeks of treatment and a mean increase of 87 mg/dL from baseline at 8 weeks of treatment. While on treatment, a total of 9 out of 63 subjects experienced treatment-emergent Grade 3 hypertriglyceridemia, and a total of 4 subjects experienced treatment-emergent Grade 4 hypertriglyceridemia. Data from study GS-US-384-3914 Cohort 10, which treated subjects with GS-0976 (20 mg) + fenofibrate (48 mg), showed a mean increase in triglycerides of 47 mg/dL from baseline at 4 weeks of treatment and a mean increase of 42 mg/dL from baseline at 8 weeks of treatment. While on treatment, 1 subject experienced treatment-emergent Grade 3 hypertriglyceridemia. However, in study GS-US-384-3914 Cohort 11, subjects who were treated with the high-dose fenofibrate (145 mg daily) co-administered with GS-0976 (20 mg) showed no increase in triglycerides from

baseline at 4 weeks and 8 weeks of treatment, and no subjects experienced treatment-emergent Grade 3 or 4 hypertriglyceridemia while on treatment.

Amendment 12 of this study adds two cohorts (12 and 13) to evaluate the effects of pre-treatment with triglyceride-lowering therapies, Vascepa® 4 g or fenofibrate 145 mg, on serum triglycerides in patients treated with GS-0976 + GS-9674. Treatment with Vascepa or fenofibrate will be initiated two weeks prior to dosing with GS-0976 and GS-9674 with the goal of lowering pre-treatment triglyceride concentrations in order to mitigate possible increases in triglycerides that result from combination treatment with GS-0976 and GS-9674. Based on prior studies, the effect of GS-0976 and GS-9674 on serum triglycerides plateaus after approximately 4 weeks of treatment. To ensure any trend in triglycerides is captured in this study, treatment will be maintained for 6 weeks.

1.8.1. Rationale for Dose Selection of Selonsertib

SEL 18 mg once daily was selected for evaluation in this study based on a combination of safety and efficacy data in the Phase 2 NASH study (GS-US-384-1497) as well as PK/PD modeling of predicted inhibition of p38 phosphorylation. In study GS-US-384-1497, SEL 6 mg and 18 mg (± SIM 125 mg) for 24 weeks were evaluated. While both doses demonstrated a ≥ 1-stage decrease in NASH CRN fibrosis stage from baseline at a rate higher than subjects treated with SIM alone or compared to historical placebo response rates, 18 mg (± SIM 125 mg) had a slightly higher response rate than 6 mg (± SIM 125 mg). An exposure-response relationship was identified for SEL exposure and % change from baseline of blood phosphorylated p38 measured in Phase 2 studies in PAH and DKD subjects after administration of SEL 2 mg, 6 mg, or 18 mg once daily. Utilizing this model, plasma SEL AUC_{tau} observed in the NASH subjects after administration of SEL 18 mg ± SIM 125 mg was associated with 78% (7.5%) of maximal inhibition (E_{max}) of phosphorylated p38 [mean (%CV)]. Across the clinical development program, SEL has been well-tolerated in Phase 1 and Phase 2 studies up to 48 weeks in duration with no clear dose-safety relationships for incidences or severity of AEs or laboratory abnormalities. Thus, the efficacy and safety profile of SEL support dosing of 18 mg once daily in this study.

1.8.2. Rationale for Dose Selection of GS-0976

The dose of GS-0976 chosen for evaluation in this study, 20 mg PO daily, is supported by the safety, tolerability and effects of GS-0976 on DNL from studies 0976-101, 0976-102, and 0976-103 described in the IB. In these studies, single doses of GS-0976 up to 1000 mg or multiple daily doses (10 days) of GS-0976 up to 200 mg were administered to healthy subjects and a single dose of 20 mg of GS-0976 resulted in a mean inhibition of fractional DNL of 71%. 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 and 0976-102 (Please refer to the IB for additional information), GS-0976 exposures in non-cirrhotic subjects are expected to remain > 45 to 84-fold lower than the GS-0976 exposures observed at the NOAELs in the 13-week rat and dog studies, respectively. Based on preliminary data from Study GS-US-426-3988, GS-0976 exposures in

subjects with mild hepatic impairment (CPT A) are expected to remain > 20 to 37-fold lower than the GS-0976 exposures observed at the NOAELs in the 13-week rat and dog studies, respectively. Based on preliminary PK data in subjects with mild hepatic impairment and the overall safety profile of GS-0976, dose adjustments are not considered necessary for subjects with compensated cirrhosis in this study.

1.8.3. Rationale for Dose Selection of GS-9674

In the Phase 1 study GS-US-402-1851, GS-9674 was tested at doses ranging from 10 to 300 mg once daily for up to 14 days and was well tolerated. Across the range of GS-9674 doses evaluated, doses ≥ 30 mg provided comparable intestinal FXR agonism as assessed by increases in FGF19 exposure. Food, by slowing oral absorption of GS-9674, resulted in prolonged elevation of plasma FGF19 concentrations. Exposure-response relationships showed that changes in C4 exposure are negatively correlated with changes in exposure of FGF19 and GS-9674. Based on these results, a GS-9674 dose of 30 mg with food has been selected for this study as it is expected to provide sufficient enteral FXR agonism and result in histologic improvements in subjects with NASH. At a dose of 30 mg once daily in subjects with normal hepatic function or mild hepatic impairment, exposure margins relative to preclinical NOAEL exposures for both parent and metabolite are expected to remain adequate. Based on the preliminary PK and PD data in subjects with mild hepatic impairment as well as the overall safety profile of GS-9674, dose adjustments are not considered necessary in subjects with compensated cirrhosis in this study.

1.8.4. Rationale for Dose Selection of Selonsertib, GS-9674, and/or GS-0976 in Combination

SEL, GS-9674, and/or GS-0976 can be coadministered without dose modification, based on the available preclinical and clinical safety information on each single agent and the combination as well as the PK results from study GS-US-402-2101, showing no clinically meaningful changes in SEL, GS-9674, and GS-0976 exposure when coadministered (Please refer to GS-9674 IB for additional information). Based on the lack of PK DDIs between each of the pairwise combinations, there is no expected DDI in the triple combination of SEL, GS-9674, and GS-0976. Thus, doses of 18 mg SEL once daily, 30 mg GS-9674 once daily, and/or 20 mg GS-0976 once daily were selected for evaluation in combination in this study.

1.8.5. Rationale for Dose Selection of GS-0976 + Fenofibrate in Combination

Data supporting the safety of fibrates in patients with advanced hepatic fibrosis are limited. The majority of the available data come from small studies of patients with primary biliary cholangitis (PBC) who have an inadequate response to ursodeoxycholic acid {Cheung 2016, Levy 2011}. Published data regarding safety in patients with bridging fibrosis and compensated cirrhosis due to NASH are lacking. In Gilead's previous studies with simtuzumab in subjects with advanced fibrosis due to NASH (GS-US-321-0105, GS-US-321-0106), 32 out of 477 subjects (6.7%) were treated with fibrates during the trials. No clear safety signals were attributed to fibrate therapy in these subjects. The doses of fenofibrate, 48 mg and 145 mg, to be coadministered with GS-0976 20 mg in Cohorts 10 and 11 of this study to overcome triglyceride

elevations induced by ACC inhibition and further increase fatty acid oxidation and cholesterol metabolism are based on the range of recommended starting doses of fenofibrate for treatment of hypertriglyceridemia, which will be present in all subjects at baseline. No pharmacokinetic interaction is expected between fenofibrate and GS-0976 based on a combination of non-clinical and clinical drug-drug interaction information. Cohorts 10 and 11 of this study will enroll subjects with bridging fibrosis or compensated cirrhosis. As fenofibrate is primarily hydrolyzed by esterases and excreted primarily in the urine as fenofibric acid and fenofibric acid glucuronide, compensated cirrhosis is not expected to alter the exposure of fenofibric acid or its glucuronide conjugate. The dose-ranging of fenofibrate in Cohorts 10 and 11 in this study will allow for the selection of a dose of fenofibrate that is most safe and effective at prevention of hypertriglyceridemia in subjects with advanced fibrosis due to NASH receiving treatment with GS-0976 20 mg.

1.8.6. Rationale for Dose Selection of GS-0976 + GS-9674 + Vascepa® in Combination

The dose of Vascepa® to be administered in Cohort 13 was selected from a controlled clinical trial that showed a reduced risk of cardiovascular events among patients with hypertriglyceridemia and cardiovascular risk factors that were treated with this dose of Vascepa® compared with placebo (refer to section 1.7). The combination of GS-0976 + GS-9674 at the specified doses was selected based on data showing this regimen to be safe and potentially effective when co-administered in prior cohorts of this study. Vascepa® is not expected to have any drug interactions when given in combination with GS-0976 + GS-9674 or affect the pharmacokinetics of either compound.

1.8.7. Rationale for Dose Selection of GS-0976 + GS-9674 + Fenofibrate in Combination

The dose selection for this combination treatment was selected as these have been shown to be safe and effective in prior cohorts. The dose of fenofibrate was selected based on data from Cohorts 10 and 11 (refer to section 1.8).

1.8.8. Rationale for Study Population

The progression from NAFLD to NASH to cirrhosis occurs over decades. The highest levels of morbidity and mortality are found in NASH patients with advanced fibrosis and cirrhosis {Ekstedt 2014, Yeh 2014}. Thus, targeting interventions to help this population would have the greatest impact on morbidity and mortality. Inclusion criteria for this study were developed in order to enrich this small proof-of-concept study with subjects who have definite inflammatory and fibrotic processes that can be measured, including those with compensated cirrhosis.

Specifically, all subjects in Cohorts 1 through 6 and 9 will have a clinical diagnosis of NAFLD, evidence of ≥ 10% hepatic steatosis on MRI-PDFF {Bannas 2015}, and increased liver stiffness on MRE (≥ 2.88 kPa) {Chen 2011}, or histologic confirmation of NASH with moderate to severe fibrosis. Previous studies have shown that patients with NAFLD and increased liver stiffness on MRE have a high probability of NASH on liver biopsy. For example, Chen et al.

reported that an MRE liver stiffness cut-off of ≥ 2.90 kPa was 83% sensitive, 82% specific, and had an area under the receiver operating characteristic curve (AUROC) of 0.93 and positive predictive value of 88% for the differentiation of simple steatosis from NASH on biopsy. Moreover, in a meta-analysis of MRE for the diagnosis of NAFLD-related fibrosis {Singh 2016}, a liver stiffness ≥ 2.88 kPa optimally identified the presence of at least stage 1 fibrosis (AUROC 0.86). Based on these criteria, subjects enrolled in Cohorts 1 through 6 and 9 have a high probability of NASH with fibrosis, a population with a large unmet medical need {Loomba 2014}. With safety and PK data for GS-9674 and GS-0976 in subjects with hepatic impairment, these two compounds will be tested as monotherapy in patients with CPT A cirrhosis in Cohorts 7 (GS-0976) and 8 (GS-9674). For Cohorts 10 and 11, the diagnosis of advanced fibrosis will be based on a clinical diagnosis of NAFLD, a historical liver biopsy, or noninvasive tests of fibrosis (MRE) that are predictive of bridging fibrosis or compensated cirrhosis {Loomba 2014, Munteanu 2016, Singh 2016}. Previous clinical trials with GS-0976 20 mg have demonstrated that subjects most at risk for Grade 3-4 hypertriglyceridemia have baseline elevations of triglycerides >150 mg/dL, with an increased risk for those with baseline levels >250 mg/dL. For this reason, Cohorts 10 and 11 will have a 60:40 ratio of patients that meet these baseline triglyceride thresholds. For Cohorts 12 and 13, the diagnosis of NASH/NAFLD will be based on clinical features along with criteria for metabolic syndrome or evidence of fibrosis based on liver biopsy or liver stiffness by FibroScan® or MRE. Since the objective of Cohorts 12-13 is to evaluate the effects of pre-treatment with either fenofibrate or Vascepa® on serum triglycerides in the setting of GS-0976 + GS-9674 combination treatment, patients in Cohorts 12 and 13 must have hypertriglyceridemia (triglycerides ≥150 and <500 mg/dL) during Screening.

1.9. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

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

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3. STUDY DESIGN

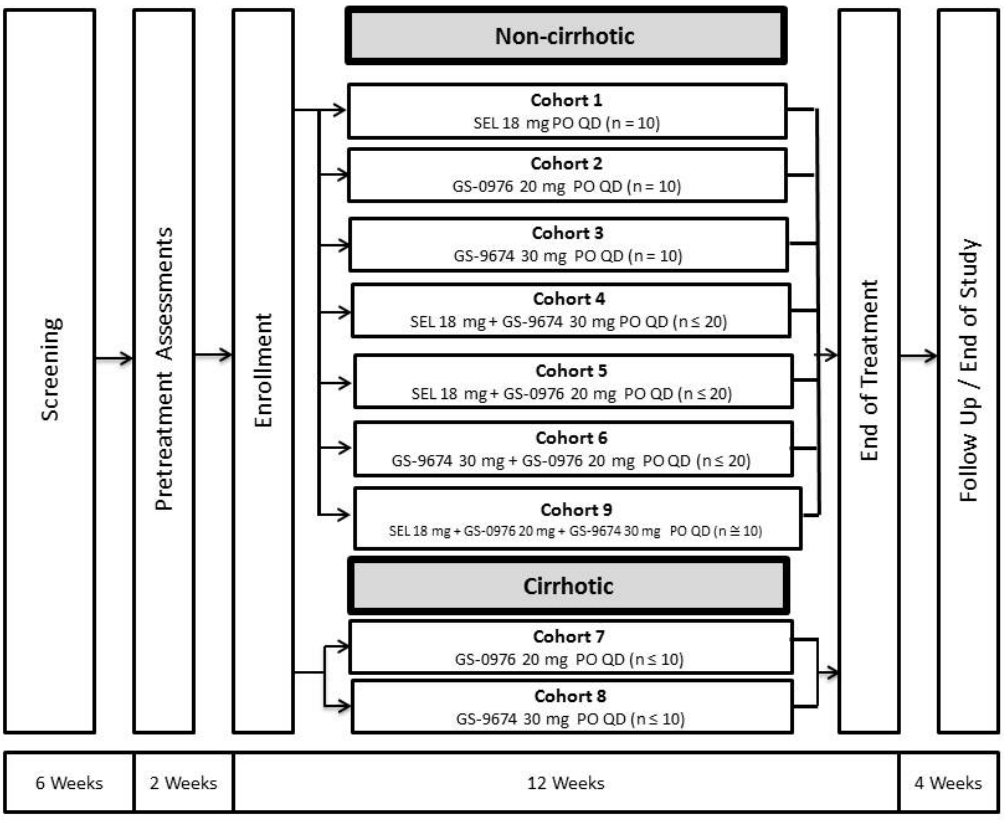
3.1. Study Design

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

3.2. Treatment Plan and Regimen

Approximately 210 subjects total will be enrolled into one of 13 cohorts.

Eligible subjects for Cohorts 1-9 will be enrolled to receive treatment with SEL, GS-0976, GS-9674; the combination of SEL and GS-9674, SEL and GS-0976, GS-0976 and GS-9674; or SEL, GS-0976 and GS-9674 for 12 weeks as shown in the figure below.



Cohort 1 (SEL) will consist of 10 enrolled subjects

Cohort 2 (GS-0976) will consist of 10 enrolled subjects

Cohort 3 (GS-9674) will consist of 10 enrolled subjects

Cohort 4 (SEL + GS-9674) will consist of up to 20 enrolled subjects

Cohort 5 (SEL + GS-0976) will consist of up to 20 enrolled subjects

Cohort 6 (GS-0976 + GS-9674) will consist of up to 20 enrolled subjects

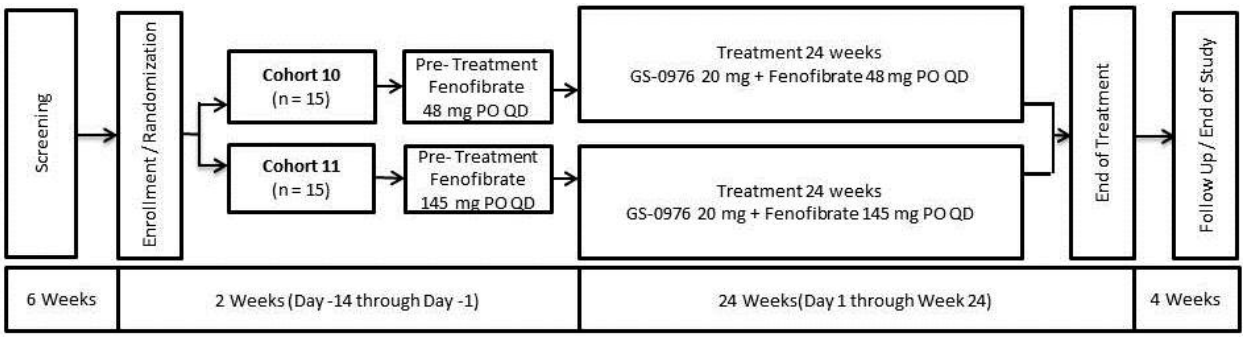
Cohort 7 (GS-0976) will consist of up to 10 enrolled subjects with CPT A cirrhosis

Cohort 8 (GS-9674) will consist of up to 10 enrolled subjects with CPT A cirrhosis

Cohort 9 (SEL + GS-0976 + GS-9674) will consist of approximately 10 enrolled subjects

Cohorts 1 through 6 and 9 will be enrolled sequentially while Cohorts 7 and 8 will be randomized in parallel. The Biostatistics department at Gilead will generate a randomization list for cirrhotic subjects who qualify for Cohorts 7 and 8. Once subjects are deemed eligible and before they start kinetic labeling (Day -14), the site will contact the Clinical Operations team at Gilead by email or phone, and the Clinical Operations team will utilize the proper randomization list to assign the subject to the appropriate cohort.

For Cohorts 10 and 11, eligible subjects will be randomized to receive pretreatment with fenofibrate 48 mg or fenofibrate 145 mg from Day -14 to Day -1 and will be treated with GS-0976 20 mg and fenofibrate 48 mg or GS-0976 20 mg and fenofibrate 145 mg for 24 weeks as shown in the figure below.

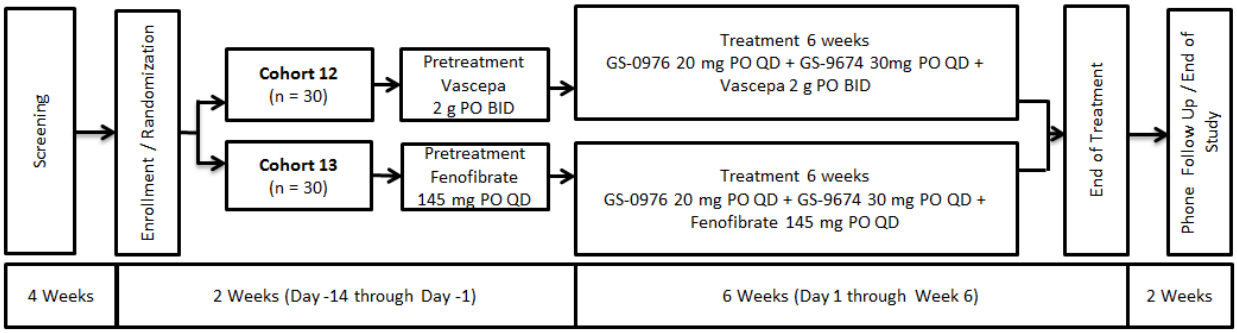


Approximately 30 subjects will be randomized (1:1) into either Cohort 10 or 11; randomization will be stratified by (1) screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]), and (2) fibrosis stage [F3 defined by liver biopsy or screening MRE with liver stiffness < 4.67 kPa or F4 defined by liver biopsy or screening MRE with liver stiffness ≥ 4.67 kPa. Approximately 60% of subjects in each Cohort should have cirrhosis (F4)

based on Inclusion Criteria 5. Approximately 60% subjects in each cohort should have screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL as below:

- Cohort 10 (GS-0976 20 mg + Fenofibrate 48 mg) will consist of 15 subjects:
    - Approximately 9 subjects with Screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL
    - Approximately 6 subjects with Screening serum triglycerides ≥ 250 mg/dL and < 500 mg/dL
- Cohort 11 (GS-0976 20 mg + Fenofibrate 145 mg) will consist of 15 subjects:
    - Approximately 9 subjects with Screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL
    - Approximately 6 subjects with Screening serum triglycerides ≥ 250 mg/dL and < 500 mg/dL

For Cohorts 12 and 13, eligible subjects will be randomized to receive pretreatment with Vascepa® 2 g twice daily or fenofibrate 145 mg once daily from Day -14 to Day -1 and will be treated with GS-0976 20 mg once daily, GS-9674 30 mg once daily, and Vascepa® 2 g twice daily; or GS-0976 20 mg once daily, GS-9674 30 mg once daily, and fenofibrate 145 mg once daily for 6 weeks as shown in the figure below.



Approximately 60 subjects will be randomized (1:1) into either Cohorts 12 or 13. Randomization will be stratified by screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]).

- Cohort 12 (GS-0976 20 mg once daily + GS-9674 30 mg once daily + Vascepa® 2 g twice daily) will consist of 30 subjects
- Cohort 13 (GS-0976 20 mg once daily + GS-9674 30 mg once daily+ fenofibrate 145 mg once daily) will consist of 30 subjects

[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]

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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This trial will enroll approximately 230 subjects with NAFLD/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 (Cohorts 1-9) and ≥ 18 years (Cohorts 10-13) of age; inclusive based on the date of the Screening Visit;

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

3. For Cohorts 1 through 6 and 9, subjects must meet all of the following conditions (a-d OR e&f):

    a) Clinical diagnosis of NAFLD,

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

    c) Screening MRI-PDFF with ≥ 10% steatosis,

    d) Screening MRE with liver stiffness ≥ 2.88 kPa,

OR

    e) A historical liver biopsy within 12 months of Screening consistent with NASH (defined as the presence of steatosis, inflammation, and ballooning) with stage 2-3 fibrosis according to the NASH CRN classification (or equivalent),

AND

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

4. For Cohorts 7 and 8, subjects must have a clinical diagnosis of NAFLD and have at least one of the following criteria (a-d):

    a) Screening MRE with liver stiffness ≥ 4.67 kPa,

    b) A historical FibroScan® ≥ 14 kPa within 6 months of Screening,

    c) Screening FibroTest® ≥ 0.75,

    d) A historical liver biopsy consistent with stage 4 fibrosis according to the NASH CRN classification (or equivalent);

5. For Cohorts 10 and 11, subjects must have a clinical diagnosis of NAFLD and the following criteria:

    a) At least two criteria for metabolic syndrome modified from the NCEP ATP III Guidelines, at Screening:

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

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

        iii. Fasting triglycerides ≥ 150 mg/dL,

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

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

AND one of the following criteria:

    b) A historical liver biopsy within 6 months of Screening consistent with NASH and bridging fibrosis (F3) or within 12 months of Screening consistent with NASH and compensated cirrhosis (F4) in the opinion of the investigator,

    c) Screening liver stiffness by MRE ≥ 3.64 kPa,

    d) Screening liver stiffness by FibroScan® ≥ 9.9 kPa;

6. For Cohorts 12 and 13, subjects must have a clinical diagnosis of NAFLD/NASH and the following criteria:

    a) At least two criteria for metabolic syndrome modified from the NCEP ATP III Guidelines, at Screening:

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

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

        iii. Fasting triglycerides ≥ 150 mg/dL,

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

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

OR one of the following criteria:

    b) A historical liver biopsy within 6 months of Screening consistent with NASH for subjects without compensated cirrhosis (F4); or within 12 months of Screening consistent with NASH for subjects with compensated cirrhosis (F4) in the opinion of the investigator,

    c) A historical MRE with liver stiffness ≥ 2.88 kPa within 6 months of Screening,

    d) A historical FibroScan® with liver stiffness ≥ 9.9 kPa within 6 months of Screening,

AND

    e) No documented weight loss > 5% between the date of the historical liver biopsy, historical MRE, or historical Fibroscan and Screening;

7. A Platelet count ≥ 100,000/µL;

8. Serum creatinine < 2 mg/dL (Cohorts 1-9) at Screening;

9. Estimated glomerular filtration rate (eGFR) ≥ 80 mL/min (Cohorts 10-11) or ≥ 60 mL/min (Cohorts 12-13), as calculated by the Cockcroft-Gault equation at Screening;

10. For Cohorts 10-13, serum triglyceride level ≥ 150 mg/dL at Screening;

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

12. 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 90 days following the last dose of study drug as described in Appendix 3;

13. Male subjects must agree to use condoms during intercourse from screening through the study completion and for 90 days following the last dose of study drug;

14. Male subjects must refrain from sperm donation from screening through at least 90 days following the last dose of study drug;

15. Female subjects must refrain from egg donation or harvest for 90 days after last dose of study drug;

16. Must be able to read and complete Quality of Life questionnaires independently (Cohorts 1-11);

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

4.3. Exclusion Criteria

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

1. Pregnant or lactating females;

2. Other causes of liver disease including autoimmune, viral, and alcoholic liver disease;

3. Any history of decompensated liver disease, including ascites, hepatic encephalopathy, or variceal bleeding;

4. For Cohorts 7-8 and 10-13, Child-Pugh-Turcotte (CPT) score > 6 (Appendix 4) at Screening, unless due to an alternative etiology such as Gilbert's syndrome or therapeutic anticoagulation;

5. History of liver transplantation;

6. History of hepatocellular carcinoma;

7. Weight reduction surgery in the past 2 years or planned during the study;

8. Documented weight loss > 5% between the date of the historical liver biopsy and Screening, if applicable;

9. BMI < 18 kg/m^2;

10. ALT > 5 x ULN at Screening;

11. For Cohorts 10-13, HbA1c ≥ 9.5% (or serum fructosamine ≥ 381 μmol if HbA1c is unable to be resulted) at Screening;

12. For Cohorts 10-13, hemoglobin ≤ 10.6 g/dL at Screening;

13. INR > 1.2 (Cohorts 1-9) or INR > 1.4 (Cohorts 10-13) at Screening, unless on anticoagulation therapy;

14. Total bilirubin > 1x ULN (Cohorts 1 through 6 and 9), >1.5 x ULN (Cohorts 7 and 8), or >1.3 x ULN (Cohorts 10-13) except in confirmed cases of Gilbert's syndrome;

15. Triglycerides ≥ 500 mg/dL (Cohorts 5-8 and 10-13) or ≥ 250 mg/dL (Cohort 9) at Screening;

16. Model for End-Stage Liver Disease (MELD) score > 12 at Screening (Cohorts 10-13), unless due to an alternate etiology such as therapeutic anticoagulation;

17. Chronic hepatitis B (HBsAg positive);

18. Chronic hepatitis C (HCV RNA positive); Subjects cured of HCV infection less than 2 years prior to the Screening visit are not eligible (Cohorts 10-13);

19. HIV Ab positive;

20. Presence of gallstones within 6 months of Screening (Cohorts 10-13);

21. 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/30mL measure of 40% proof alcohol);

22. 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;

23. 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;

24. History of intestinal resection of the extent that would result in malabsorption;

25. Use of any prohibited concomitant medications as described in Section 5.8;

26. History of a malignancy within 5 years of screening with the following exceptions:

    a) Adequately treated carcinoma in situ of the cervix,

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

27. 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;

28. Participation in another investigational study of a drug or device within 1 month prior or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Screening;

29. Concurrent participation in another therapeutic clinical study;

30. Known hypersensitivity to study drugs, the metabolites, or formulation excipients;

31. 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 or medical condition;

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

33. Contraindications to MRI scanning (e.g., presence of permanent pacemakers, implanted cardiac devices, etc.) **(**Cohorts 1-11);

34. For Cohorts 10 -13, any contraindication to fenofibrate, per the approved package insert, with the exception of advanced liver fibrosis;

35. For Cohorts 12 and 13, any contraindication to Vascepa®, per the approved package insert;

36. For Cohorts 12 and 13, history of acute or chronic pancreatitis;

37. For Cohorts 12 and 13, known hypersensitivity to fish and/or shellfish;

38. For Cohorts 12 and 13, poorly controlled hypertension despite anti-hypertensive therapy.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization

Cohorts 1 through 6 and 9 will be enrolled sequentially without any randomization. Cohorts 7 and 8 will be enrolled in parallel and randomized for this purpose. For Cohorts 10 and 11, randomization will be stratified by (1) screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]), and (2) fibrosis stage [F3 defined by liver biopsy or screening MRE with liver stiffness < 4.67 kPa or F4 defined by liver biopsy or screening MRE with liver stiffness ≥ 4.67 kPa]. For Cohorts 12 and 13, randomization will be stratified by screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]). The Biostatistics department at Gilead will generate a randomization list for subjects who qualify for randomized cohorts.

Further details of the randomization can be found in the Randomization Schedule document.

5.2. Description and Handling of Selonsertib

5.2.1. Formulations

5.2.1.1. Selonsertib Tablets

For Cohorts 1, 4, 5 and 9, SEL will be supplied as round, plain-faced, white film-coated tablets containing 18 mg of SEL. In addition to the active ingredient, SEL tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide and talc.

5.2.2. Packaging and Labeling

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

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

5.2.3. Storage and Handling

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

Until dispensed to the subjects, all study drug(s) should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drug 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. Description and Handling of GS-0976

5.3.1. Formulations

5.3.1.1. GS-0976 Capsules and Tablets

For Cohort 2, GS-0976 will be supplied as white opaque size 0 hard gelatin capsules containing 10 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.

For Cohorts 5-7 and 9-13, GS-0976 will be supplied as round, plain-faced, film-coated, white tablets containing 20 mg of GS-0976. In addition to the active ingredient, GS-0976 tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc, which are common pharmaceutical excipients.

5.3.2. Packaging and Labeling

For Cohort 2, GS-0976 capsules are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 200 capsules. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

For Cohorts 5-7 and 9-13, GS-0976 tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum faced liner.

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

5.3.3. Storage and Handling

GS-0976 capsules and tablets should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

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

5.4. Description and Handling of GS-9674

5.4.1. Formulation

5.4.1.1. GS-9674 Tablets

For Cohort 3, GS-9674 will be supplied as round, plain-faced, film-coated orange tablets containing 10 mg (as free form equivalent) of GS-9674. In addition to the active ingredient, GS-9674 tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium stearate, and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide and ferrosoferric oxide.

For Cohorts 4, 6, 8 and 9, GS-9674 will be supplied as round, plain-faced, film-coated orange tablets containing 30 mg (as free form equivalent) of GS-9674. In addition to the active ingredient, GS-9674 tablets contain the following inactive ingredients: microcrystalline cellulose, mannitol, crospovidone, magnesium stearate and film-coating material comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide and ferrosoferric oxide.

For Cohorts 12 and 13, GS-9674 will be supplied as round, film-coated green tablets, debossed with “GSI” on one side of the tablet and “30” on the other side of the tablet, and containing 30 mg (as free form equivalent) of GS-9674. In addition to the active ingredient, GS-9674 tablets contain the following inactive ingredients: microcrystalline cellulose, mannitol, crospovidone, magnesium stearate and film-coating material composed of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, and ferrosoferric oxide.

5.4.2. Packaging and Labeling

GS-9674 tablets are packaged in white, high-density polyethylene (HDPE) bottle. Each bottle contains 30 tablets, a silica gel desiccant, and polyester packing material. Each bottle is enclosed

with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

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

5.4.3. Storage and Handling

GS-9674 tablets should be stored below 30 °C (86 °F). Storage conditions are specified on the label.

Until study drug tablets are 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, the drug products 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 GS-9674 tablets.

5.5. Description and Handling of Fenofibrate

5.5.1. Formulation

5.5.1.1. Fenofibrate Tablets

Commercially available fenofibrate 48 mg and 145 mg tablets will be used for the study. Information regarding the formulation of commercially available fenofibrate can be found in the prescribing information.

5.5.2. Packaging and Labeling

Commercially available fenofibrate will be used for the study. Fenofibrate is packaged in bottles of 90 tablets. Fenofibrate to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.5.3. Storage and Handling

Commercially available fenofibrate will be used for the study. Further information regarding storage and handling is available in the Prescribing Information for commercial products.

5.6. Description and Handling of Vascepa®

5.6.1. Formulation

5.6.1.1. Vascepa® Capsules

Commercially available Vascepa® 1g capsules will be used for this study. Information regarding the formulation of commercially available Vascepa® can be found in the prescribing information.

5.6.2. Packaging and Labeling

Commercially available Vascepa® will be used for the study. Vascepa® is packaged in bottles of 120 capsules. Vascepa® to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.6.3. Storage and Handling

Commercially available Vascepa® will be used for the study. Further information regarding storage and handling is available in the Prescribing Information for commercial products.

5.7. Dosage and Administration

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

5.7.1. Selonsertib

SEL tablets will be provided by Gilead Sciences. Subjects will take one tablet of SEL (18 mg) once daily at approximately the same time each morning. Study drug should be swallowed whole with water and may be taken with or without food. A dose will be considered missed if the subject cannot take the dose within 12 hours of their regular dosing time. If a subject misses a dose, the subject should take their next dose at the regular dosing time.

5.7.2. GS-0976

GS-0976 capsules and tablets will be provided by Gilead Sciences. For Cohort 2, subjects will take two capsules of GS-0976 (10 mg) once daily at approximately the same time each morning. For Cohort 7, subjects will take 1 tablet of GS-0976 (20 mg) once daily at approximately the same time each morning. Study drug should be swallowed whole with water and may be taken with or without food. A dose will be considered missed if the subject cannot take the dose within 12 hours of their regular dosing time. If a subject misses a dose, the subject should take their next dose at the regular dosing time.

5.7.3. GS-9674

GS-9674 tablets will be provided by Gilead Sciences. For Cohort 3, subjects will take three tablets of GS-9674 (10 mg) once daily at approximately the same time each morning. For Cohort 8, subjects will take one tablet of GS-9674 (30 mg) once daily at approximately the same time each morning. Study drug should be swallowed whole with water and should be taken with 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.

5.7.4. Selonsertib + GS-9674

For Cohort 4, SEL and GS-9674 tablets will be provided by Gilead Sciences. Subjects will take one tablet of SEL (18 mg) and one tablet of GS-9674 (30 mg) once daily at approximately the same time each morning. Study drugs should be swallowed whole with water and should be taken with 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.

5.7.5. Selonsertib + GS-0976

For Cohort 5, SEL and GS-0976 tablets will be provided by Gilead Sciences. Subjects will take one tablet of SEL (18 mg) and one tablet of GS-0976 (20 mg) once daily at approximately the same time each morning. Study drugs should be swallowed whole with water and can 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.

5.7.6. GS-0976 + GS-9674

For Cohort 6, GS-0976 and GS-9674 tablets will be provided by Gilead Sciences. Subjects will take one tablet of GS-0976 (20 mg) and one tablet of GS-9674 (30 mg) once daily at approximately the same time each morning. Study drugs should be swallowed whole with water and should be taken with 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.

5.7.7. SEL + GS-0976 + GS-9674

For Cohort 9, SEL, GS-0976 and GS-9674 will be provided by Gilead Sciences. Subjects will take one tablet each of SEL (18 mg), GS-0976 (20 mg), and GS-9674 (30 mg) once daily at approximately the same time each morning. Study drugs should be swallowed whole with water and should be taken with 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.

5.7.8. GS-0976 + Fenofibrate

GS-0976 and fenofibrate will be provided by Gilead Sciences. For Cohort 10, subjects will take one tablet of GS-0976 (20 mg) and one tablet of fenofibrate (48 mg) once daily at approximately the same time each morning. For Cohort 11, subjects will take one tablet of GS-0976 (20 mg) and one tablet of fenofibrate (145 mg) 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.

5.7.9. GS-0976 + GS-9674 + Vascepa®

For Cohort 12, GS-0976, GS-9674, and Vascepa® will be provided by Gilead Sciences. Subjects will take one tablet of GS-0976 (20 mg) once daily, one tablet of GS-9674 (30mg) once daily, and 2 capsules of Vascepa® (1 g) two times daily at approximately the same time each day. Vascepa® should be swallowed whole with water and should be taken with food. GS-9674 and GS-0976 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.

5.7.10. GS-0976 + GS-9674 + Fenofibrate

For Cohort 13, GS-0976, GS-9674, and fenofibrate will be provided by Gilead Sciences. Subjects will take one tablet of GS-0976 (20 mg), one tablet of GS-9674 (30 mg), and one tablet of fenofibrate (145 mg) 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.

5.8. 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.

Subjects on Vitamin E ≥ 800 IU/day must be on a stable dose (defined as no changes in prescribed dose, new Vitamin E containing medications, or discontinuation) for at least 6 months prior to the Screening Visit.

Any investigational medication (e.g., obeticholic acid, elafibranor, and cenicriviroc) within 30 days or within 5 half-lives prior to Screening and through follow-up is prohibited.

The following medications are prohibited for all treatment groups within 30 days prior to Screening through Follow-Up Visit:

- The use of any investigational device,
- Chronic systemic immunosuppressant's including but not limited to: corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab). Use for ≤ 2 weeks total is allowed,
- Hematologic stimulating agents (e.g., erythropoiesis-stimulating agents [ESAs]; granulocyte colony stimulating factor [GCSF]; thrombopoietin [TPO] mimetics),
- Any medication or supplement prescribed for weight loss,
- Fibrate or fish oil treatment (not including the fenofibrate or Vascepa® administered as study drugs in this protocol); subjects can be screened after washout period of 30 days (Cohorts 10-13).

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

5.8.1. Prohibited Medications for Use with Administration of Selonsertib

Caution should be exercised when co-administering sensitive P-gp substrates with narrow therapeutic index with SEL as it may increase the concentrations of these agents. The investigator should review the prescribing information of the concomitant medication for guidance on co-administration with a weak P-gp inhibitor.

Strong CYP3A4 inducers may decrease the exposure of SEL and could lead to decreased efficacy. Use of strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) is prohibited from 28 days prior to Day 1 through end of treatment.

Examples of representative medications which are prohibited from 28 days prior to Day 1 up to and including the day of the last dose of study drug and those to be used with caution are listed below in Table 5-1:

Table 5-1. List of Medications Prohibited and to Be Used with Caution

Drug Class	Agents Disallowed	Agents to be used with Caution
Anticonvulsants[a]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials[a]	Rifampin, Rifabutin, Rifapentine	
Cardiac Medications[b]		Digoxin[c], Ranolazine, Dabigatran etexilate, Aliskiren
Herbal/Natural Supplements[a]	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	

a May result in a decrease in the concentration of study drug.
b SEL may increase the exposure of these drugs.
c For subjects on digoxin at start of study: Obtain digoxin level prior to starting SEL, reduce dose of digoxin by 15-30%, and follow digoxin level at the Week 1 Visit with digoxin level checks during the study period per investigator discretion (none to as frequent as needed).

5.8.2. Prohibited Medications for Use with Administration of GS-0976

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters P-gp or OATP 1B1 or 1B3) 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 Day 1 through end of treatment are listed below in Table 5-2.

Table 5-2. List of Disallowed Medications

Drug Class	Agents Disallowed	Agents to be used with Caution
Antibiotics	Azithromycin, Clarithromycin, Erythromycin	
Anticonvulsants[a]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials[a]	Rifamycins, Isoniazid	
Bile acid sequestrants[b]		cholestyramine, colestipol, colesevelem
Cardiac Medications	Bosentan	
Herbal/Natural Supplements[a]	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
Other	Modafinil	

a May result in a decrease in the concentrations of study drugs.
b Bile acid sequestrants are permitted but may not be taken within 4 hours (before or after) study drug administration.

5.8.3. Prohibited Medications for Use with Administration of GS-9674

The following medications are prohibited from 28 days prior to Day 1 up to and including the day of the last dose of study drug:

- Vitamin E,
- Hematologic stimulating agents (e.g., erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics),
- Chronic systemic immunosuppressant's including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab). Use for < 2 weeks total is allowed,
- Investigational agents or devices for any indication,
- Concomitant use of certain medications or herbal/natural supplements (potent inhibitors of OATP or potent or moderate inducers of OATP, CYP2C8, P-gp, or CYP3A) with study drug(s) may result in PK interactions leading to increases or decreases in exposure of study drug. Examples of representative medications which are prohibited from 28 days prior to Day 1 up to and including the day of the last dose of study drug, are listed below in Table 5-3:

Table 5-3. List of Medications Prohibited and to Be Used with Caution

Drug Class	Agents Disallowed	Use with Caution
Antibiotics		Clarithromycin, Erythromycin
Acid Reducing Agents	H2-Receptor Antagonists[a]	Antacids[b]
Anticonvulsants[c]	Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin	
Antimycobacterials[c]	Rifapentine, Rifampin	
Endothelin Receptor Antagonists	Bosentan	
Herbal/Natural Supplements[c]	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
Other	Modafinil	

a H2-Receptor Antagonists should be held 3 days prior to first dose of study drug.
b Antacids that directly neutralize stomach pH (i.e., Tums, Maalox) are permitted but may not be taken within 4 hours (before or after) study drug administration.
c May result in a decrease in the concentrations of study drug.

5.8.4. Medications to Be Used with Caution with Fenofibrate

The prescribing information for fenofibrate should be consulted for medications that are prohibited and/or to be used with caution with fenofibrate.

Examples of representative medications that should be used with caution are listed in Table 5-4.

Table 5-4. List of Medications to Be Used with Caution

Drug Class	Use with Caution
Anticoagulants[a]	Coumarin, coumadin, warfarin
Anti-gout agents[b]	Colchicine
Bile acid sequestrants[c]	Cholestyramine, colestipol, colesevelem
Lipid modifying agents[d]	Simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, pitavastatin

a Fenofibrate can increase PT/INR. Increased frequency of PT/INR assessments when the subject is started on fenofibrate is at the investigators discretion. Monitor and adjust anticoagulant dose as necessary based on prescribing information.
b Concomitant use of colchicine with fenofibrates can increase the risk of rhabodmyolysis.
c Bile acid sequestrants are permitted but may not be taken within 4 hours (before or after) study drug administration.
d Concomitant use of statins with fenofibrates can increase the risk of rhabodmyolysis.

5.8.5. Medications to Be Used with Caution with Vascepa®

The prescribing information for Vascepa® should be consulted for medications that are prohibited and/or to be used with caution with Vascepa®.

Examples of representative medications that should be used with caution are listed in Table 5-5.

Table 5-5. List of Medications to Be Used with Caution

Drug Class	Use with Caution
Anticoagulants[a]	Coumarin, coumadin, warfarin
Antiplatelets[b]	P2Y12 inhibitors, NSAIDS, SSRIs, Ibrutinib

a Omega-3 fatty acids may enhance the anticoagulant effect of anticoagulants. Patients receiving treatment with Vascepa® and drugs affecting coagulation should be monitored periodically.
b Omega-3 fatty acids may enhance the antiplatelet properties of agents with antiplatelet properties. Patients receiving treatment with Vascepa® and antiplatelet agents should be monitored periodically.

5.9. Study Drug Accountability

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

Investigational 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 kit/lot number and bottles assigned.

- Record the date, quantity of used and unused study drug bottles. Dispensing records will include the initials of the person recording the information.

5.9.1. Investigational Medicinal Product Return or Disposal

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

6. STUDY PROCEDURES

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

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.

6.2. Screening Assessments for Cohorts 1-11

6.2.1. Screening Visit (Cohorts 1-11)

Subjects will be screened within 6 weeks prior to Day -14 to determine eligibility for participation in the study. The screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences.

Screening information for subjects screened under prior protocol amendments may be used to determine eligibility and fulfill screening visit assessments for this amendment.

Subjects who previously failed screening in study GS-US-384-3914 can be re-screened in the following situation (Cohorts 1-9):

- 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 (for Cohorts 4, 5, 6 and 9: F2-F3; for Cohorts 7 and 8: F4 by NASH CRN criteria or equivalent),

- Previously screen failed due to a FibroTest® ≥ 0.75 in whom Gilbert's syndrome or hemolysis is present; a repeat FibroTest® calculated using direct bilirubin instead of total bilirubin will be used to determine eligibility (for Cohorts 4, 5, 6 and 9),

- Previously screen failed due to a FibroTest® ≥ 0.75 and with a historical liver biopsy within 12 months of Screening that does not reveal cirrhosis; FibroTest® score will not be used to determine eligibility (for Cohorts 4, 5, 6 and 9).

CCI [redacted] CCI [redacted] historical MRE and MRI-PDFF within 6 months of screening in another Gilead study (i.e., GS-US-384-3914, GS-US-402-1852, and GS-US-426-3989) may be used to determine eligibility into this study. All other screening procedures must be repeated to meet eligibility criteria.

Screening labs may be repeated once within the screening period, prior to Day -14. This will be done at the discretion of the investigator.

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

The following assessments will be performed and documented at the Screening Visit:

- Obtain written informed consent before initiation of any screening procedures
- Review and record whether the subject has met eligibility criteria
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score (for Cohorts 7, 8, 10 and 11 only)
- Obtain medical history including, but not limited to information related to the following: Type 2 Diabetes Mellitus, NAFLD, and NASH
- Review historical liver biopsy, obtained within 12 months of Screening (date of initial informed consent) for noncirrhotics and at any time for cirrhotics, to assess subject eligibility for Cohorts 1-9; or review historical liver biopsy obtained within 6 months of Screening (date of initial informed consent) for subjects with bridging fibrosis (F3) and within the last 12 months for subjects with cirrhosis (F4), to assess subject eligibility for Cohorts 10-11 (if applicable)
- Complete physical examination including height, vital signs, CCI [redacted]
- Conduct standard 12-lead ECG
- [redacted]
- [redacted]
- [redacted]

- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - Hemoglobin A1c (Cohorts 10-11)
  - CCI [redacted]
  - [redacted]
  - HIV-1, HBV & HCV Serology
  - Serum pregnancy test (only for female subjects of childbearing potential)
- Obtain urine sample for drug screen
- 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

NOTE: Screening CCI [redacted], CCI [redacted] must be performed regardless of presence of historical liver biopsy to establish a baseline value.

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

6.3. Pretreatment Assessments for Cohorts 1-11

6.3.1. Day -14 Visit (Cohorts 1-11)

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

After review of the inclusion and exclusion criteria to confirm eligibility, subjects will return to the site for the initiation of Kinetic Biomarkers – Cycle 1.

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

- Review and record whether the subject has met eligibility criteria
- Update medical history if a change has occurred during screening (Cohorts 10-11)

- Symptom driven physical examination (Cohorts 10-11)
- Record vital signs CCI [redacted] (Cohorts 10-11)
- Obtain blood samples:
  - Chemistry and hematology (Cohorts 10-11)
  - Coagulation panel (Cohorts 10-11)
  - ApoA1, ApoB (Cohorts 10-11)
  - CCI [redacted]
  - Lipidomics and NMR Lipoprofile (Cohorts 10-11)
  - Adiponectin (Cohorts 10-11)
  - Total Bile Acids (Cohorts 10-11)
  - Beta-hydroxybutyrate (Cohorts 10-11)
  - Hemoglobin A1c (Cohorts 10-11)
  - hsCRP (Cohorts 10-11)
  - CCI [redacted]
  - Kinetic Biomarkers
  - CCI [redacted]
- Obtain urine samples:
  - Kinetic Biomarkers
- Dispense deuterated water. The first dose of 50 mL deuterated water will be administered under the supervision of investigative site personnel and monitored for at least 30 minutes after for any side effects.
- Dispense fenofibrate, and provide subject with dosing instruction on appropriate dosing and administration; subject will take the Day -14 dose of study drug on-site (Cohorts 10-11)
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

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

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

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

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

- Obtain blood samples:
  - Chemistry and hematology (Cohorts 10-11)
  - Coagulation panel (Cohorts 10-11)
  - Kinetic Biomarkers
  - CCI
- Obtain urine samples
  - Kinetic Biomarkers
- Record any serious adverse events and all adverse events (related to protocol mandated procedures for Cohorts 1-9) since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

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

6.4. Treatment Assessments for Cohorts 1-11

6.4.1. Day 1 Visit (Cohorts 1-11)

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

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

- Review and record whether the subject has met eligibility criteria (Cohorts 1-9)
- Update medical history if a change has occurred during screening

- Symptom driven physical examination
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score (Cohorts 10 and 11)
- Record vital signs CCI
- QoL questionnaires (CLDQ, SF-36, &WPAI)
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - ApoA1, ApoB
  - FGF19 (Cohorts 1-9)
  - Phospho-p38 (if reagent is available) (Cohorts 1-9)
  - CCI
  - Lipidomics and NMR Lipoprofile
  - C4 (Cohorts 1-9)
  - Adiponectin
  - Total Bile Acids
  - Beta-hydroxybutyrate
  - hsCRP (Cohorts 10-11)
  - Hemoglobin A1c
  - CCI
  - Genomic sample
  - Kinetic Biomarkers
  - CCI
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Kinetic Biomarkers
- CCI

- Dispense study drug (GS-0976), and provide subject with dosing instruction on appropriate dosing and administration; subject will take the Day 1 dose of study drug on-site
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events related to protocol mandated procedures since the previous visit

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

6.4.2. Day 7 (Week 1) Visit (± 3 days) (Cohorts 1-11)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. Subjects in Cohort 5, 6, 7, 9, 10 and 11 should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

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

- Symptom driven physical examination
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score (Cohorts 10 and 11)
- Record vital signs CCI [redacted]
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - ApoA1, ApoB
  - FGF19 (Cohorts 1-9)
  - Adiponectin (Cohorts 1-9)

- Lipidomics and NMR Lipoprofile
- CCI
- C4 (Cohorts 1-9)
- Total Bile Acids
- Saliva collection for Kinetic Biomarkers (Cohorts 1-3) Refer to the laboratory manual for additional information.
- Predose Kinetic Biomarkers (Cohorts 4-11)
- CCI
- CCI
- 2 hour (± 1 hour) postdose Kinetic Biomarkers (Cohorts 5, 6, 7, 9, 10 and 11)

- Obtain urine samples for:
  - Predose Kinetic Biomarkers (Cohorts 4-11)
  - 2 hour (± 1 hour) postdose Kinetic Biomarkers (Cohorts 5, 6, 7, 9,10 and 11)
- Verify that study drug was taken correctly every day
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.4.3. Day 14 (Week 2) Visit (±1 day) (Cohorts 1-9)

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

- Obtain blood samples:
  - Kinetic Biomarkers
- Obtain urine samples:
  - Kinetic Biomarkers
- Dispense deuterated water

- Record any serious adverse events and all adverse events since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

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

6.4.4. Day 17 (± 1 day) and Day 21 (Week 3) Visits (± 1 day) (Cohorts 1-9)

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

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

- Obtain blood samples:
  - Kinetic Biomarkers
- Obtain urine samples:
  - Kinetic Biomarkers
- Record any serious adverse events and all adverse events since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

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

6.4.5. Day 28 (Week 4) Visit (± 3 days) (Cohorts 1-11)

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

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

- Symptom driven physical examination (Cohorts 1-11)
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score (Cohorts 10 and 11)
- Record vital signs CCI [redacted] (Cohorts 1-11)

- CCI [redacted]
- Obtain blood samples for:
  - Chemistry and hematology (Cohorts 1-11)
  - Coagulation panel (Cohorts 1-11)
  - Phospho-p38 (if reagent is available) (Cohorts 1-9)
  - Lipidomics and NMR Lipoprofile (Cohorts 1-11)
  - ApoA1, ApoB (Cohorts 1-11)
  - Adiponectin (Cohorts 1-9)
  - Beta-hydroxybutyrate (Cohorts 1-9)
  - Total Bile Acids (Cohorts 1-11)
  - FGF19 (Cohorts 1-9)
  - C4 (Cohorts 1-9)
  - CCI [redacted]
  - CCI [redacted]
  - Kinetic Biomarkers (Cohorts 1-9)
  - CCI [redacted]
- Collect urine samples for: (Cohorts 1-9)
  - Urine pregnancy test for females of childbearing potential only
  - Kinetic Biomarkers
- Verify that study drug was taken correctly every day (Cohorts 1-11)
- Dispense study drug (Cohorts 1-9); dispense study drug (GS-0976) (Cohorts 10-11)
- Record all concomitant medications that the subject has taken since the previous visit (Cohorts 1-11)
- Record any serious adverse events and all adverse events since the previous visit (Cohorts 1-11)

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

6.4.6. Day 35 (Week 5) Visit (± 3 days) (Cohorts 1-3)

Cohorts 1-3 subjects will collect a saliva sample at home and provide it to the site at the next visit. Refer to the laboratory manual for additional information.

6.4.7. Day 56 (Week 8) Visit (± 3 days) (Cohorts 1-11)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 10-hour fast prior to the fasted blood sample collection the next morning. Subjects in Cohorts 5, 6, 7, 9, 10 and 11 should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit. The following assessments will be performed and documented at the visit:

- Symptom driven physical examination
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score (Cohorts 10 and 11)
- Record vital signs CCI [redacted]
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - Lipidomics and NMR Lipoprofile
  - Total Bile Acids
  - ApoA1, ApoB
  - FGF19 (Cohorts 1-9)
  - C4 (Cohorts 1-9)
  - [redacted] CCI [redacted]
  - Predose Kinetic Biomarkers (Cohorts 4-11)
  - [redacted] CCI [redacted]
- 2 hour (± 1 hour) postdose Kinetic Biomarkers (for Cohorts 5, 6, 7, 9, 10 and 11)

- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Predose Kinetic Biomarkers (for Cohorts 4-11)
  - 2 hour (± 1 hour) postdose Kinetic Biomarkers (for Cohorts 5, 6, 7, 9,10 and 11)
- Verify that study drug was taken correctly every day
- Dispense study drug (Cohorts 1-9); dispense study drugs (GS-0976 and fenofibrate) (Cohorts 10-11)
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.4.8. Day 70 (Week 10) Visit (± 1 Day) (Cohorts 1-11)

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

- Obtain blood samples:
  - Kinetic Biomarkers
- Obtain urine samples:
  - Kinetic Biomarkers
- Dispense deuterated water
- Record any serious adverse events and all adverse events since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

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

6.4.9. Day 73 and Day 77 (Week 11) Visits (± 1 day) (Cohorts 1-11)

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

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

- Obtain blood samples:
  - Kinetic Biomarkers
- Obtain urine samples
  - Kinetic Biomarkers
- Record any serious adverse events and all adverse events since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

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

6.4.10. Day 84 (Week 12) Visit (±3 days) / End of Treatment (Cohorts 1-9)

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

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

- Symptom driven physical examination
- Record vital signs, CCI [redacted]
- Conduct standard 12-Lead ECG
- QoL questionnaires (CLDQ, SF-36, & WPAI)
- [redacted]
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - Phospho-p38 (if reagent is available)
  - CCI [redacted]
  - Lipidomics and NMR Lipoprofile

- Total Bile Acids
- ApoA1, ApoB
- FGF19
- C4
- Adiponectin
- Beta-hydroxybutyrate
- CCI [redacted]
- Hemoglobin A1c
- CCI [redacted]
- [redacted]
- Kinetic Biomarkers
- CCI [redacted]
- CCI [redacted]

[redacted]

- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Kinetic Biomarkers
- Verify that study drug was taken correctly every day
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

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

6.4.11. Day 84 (Week 12) Visit (±3 days) (Cohorts 10-11)

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

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

- Symptom driven physical examination
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Record vital signs, CCI
- Conduct standard 12-Lead ECG
- QoL questionnaires (CLDQ, SF-36, & WPAI)
- CCI
- CCI
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - CCI
  - Lipidomics and NMR Lipoprofile
  - Total Bile Acids
  - ApoA1, ApoB
  - hsCRP
  - Adiponectin
  - Beta-hydroxybutyrate
  - CCI
  - Hemoglobin A1c
  - CCI
  - CCI
  - Kinetic Biomarkers
  - CCI
  - CCI

- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Kinetic Biomarkers
- Dispense study drug (GS-0976)
- Verify that study drug was taken correctly every day
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

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

6.4.12. Day 91 (Week 13) Visit (± 3 days) (Cohorts 1-3)

Cohorts 1-3 subjects will collect a saliva sample at home and provide it to the site at the next visit. Refer to the laboratory manual for additional information.

6.4.13. Day 112 (Week 16) Follow up Visit (± 5 days) (Cohorts 1-9)

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

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

- Symptom driven physical examination
- Record vital signs, CCI [redacted]
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.4.14. Day 112 (Week 16) Visit (± 3 days) (Cohorts 10-11)

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

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

- Symptom driven physical examination
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Record vital signs, CCI
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - Lipidomics and NMR Lipoprofile
  - Total Bile Acids
  - ApoA1, ApoB
  - CCI
  - CCI
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Dispense study drug (GS-0976)
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.4.15. Day 126 Visit (Week 18) (± 3 days) (Cohorts 10-11)

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

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

- Obtain blood samples:
  - CCI
  - Kinetic Biomarkers
- Obtain urine samples:
  - Kinetic Biomarkers
- Dispense study drug (GS-0976)
- Dispense study drug fenofibrate
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.4.16. Day 154 (Week 22) Visit (± 1 day) (Cohorts 10-11)

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

- Obtain blood samples:
  - CCI
  - Kinetic Biomarkers
- Obtain urine samples:
  - Kinetic Biomarkers
- Dispense deuterated water
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Record any serious adverse events and all adverse events since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

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

6.4.17. Day 157 (± 1 day) and Day 161 Visits (± 1 day) (Week 23) (Cohorts 10-11)

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

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

- Obtain blood samples:
  - CCI
  - Kinetic Biomarkers
- Obtain urine samples
  - Kinetic Biomarkers
- Record any serious adverse events and all adverse events since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

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

6.4.18. Day 168 (Week 24) Visit (±3 days) / End of Treatment (Cohorts 10-11)

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

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

- Symptom driven physical examination
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Record vital signs, CCI
- Conduct standard 12-Lead ECG
- QoL questionnaires (CLDQ, SF-36, & WPAI)
- [redacted]
- [redacted]

- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - CCI
  - Lipidomics and NMR Lipoprofile
  - Total Bile Acids
  - ApoA1, ApoB
  - hsCRP
  - Adiponectin
  - Beta-hydroxybutyrate
  - CCI
  - Hemoglobin A1c
  - CCI
  - CCI
  - Kinetic Biomarker
  - CCI
  - CCI
- [redacted]
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Kinetic Biomarkers
- Verify that study drug was taken correctly every day
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

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

6.4.19. Day 196 (Week 28) Follow up Visit (± 5 days) (Cohorts 10-11)

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

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

- Symptom driven physical examination
- Record vital signs, CCI
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.4.20. Early Termination (ET) Visit (Cohorts 10 - 11)

For subjects who have completed an ET visit, the follow-up visit will be scheduled after last dose of study drugs.

When medically feasible, the medical monitor must be consulted prior to subject discontinuation.

The following procedures are to be completed at an Early Termination visit:

- Symptom driven physical examination
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Record vital signs, CCI
- Conduct standard 12-Lead ECG
- QoL questionnaires (CLDQ, SF-36, & WPAI)

- CCI [redacted]
- CCI [redacted]
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - NMR Lipoprofile
  - Total Bile Acids
  - ApoA1, ApoB
  - hsCRP
  - Adiponectin
  - Beta-hydroxybutyrate
  - CCI [redacted]
  - Hemoglobin A1c
  - CCI [redacted]
  - CCI [redacted]
  - Kinetic Biomarker
  - CCI [redacted]
  - CCI [redacted]
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
  - Kinetic Biomarkers
- Verify that study drug was taken correctly every day
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

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

6.4.21. Unscheduled Visits

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

- 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
- Obtain blood samples for:
    - Chemistry and hematology
    - Coagulation panel

6.5. STUDY PROCEDURES FOR COHORTS 12-13

6.5.1. Screening Assessments for Cohorts 12-13

6.5.1.1. Screening Visit

Subjects will be screened within 4 weeks prior to Day -14 to determine eligibility for participation in the study. The screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences.

Screening information for subjects screened under prior protocol amendments may be used to determine eligibility and fulfill screening visit assessments for this amendment.

Screening labs may be repeated once within the screening period, prior to Day -14. This will be done at the discretion of the investigator.

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the screening visit to ensure an approximate 8-hour fast prior to the fasting blood sample collection the next morning.

The following assessments will be performed and documented at the Screening Visit:

- Obtain written informed consent before initiation of any screening procedures
- Review and record whether the subject has met eligibility criteria
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Obtain medical history including, but not limited to information related to the following: Type 2 Diabetes Mellitus, NAFLD, and NASH
- Review historical liver biopsy obtained within 6 months of Screening (date of initial informed consent) for subjects without compensated cirrhosis (F4) or within the last

12 months for subjects with compensated cirrhosis (F4) to assess subject eligibility (if applicable)

- Review historical MRE and/or historical FibroScan® obtained within 6 months of screening to assess subject eligibility (if applicable)
- Complete physical examination including height, vital signs, CCI [redacted]
- Conduct standard 12-lead ECG
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - Hemoglobin A1c
  - HIV-1, HBV & HCV Serology
  - Serum pregnancy test (only for female subjects of childbearing potential)
  - CCI [redacted]
- Obtain urine sample for drug screen
- 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

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

6.5.2. Pretreatment Assessments for Cohorts 12-13

6.5.2.1. Day -14 Visit

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

The following assessments will be performed and documented at the Day -14 Visit prior to dosing:

- Review and record whether the subject has met eligibility criteria
- Update medical history if a change has occurred during screening
- Symptom driven physical examination
- Record vital signs CCI
- Obtain blood samples:
  - Chemistry and hematology
  - Coagulation panel
  - ApoA1, ApoB
  - NMR Lipoprofile
  - CCI
- Obtain urine samples:
  - Urine pregnancy test for females of childbearing potential only
- Dispense Vascepa® (Cohort 12) or fenofibrate (Cohort 13) and provide subject with dosing instruction on appropriate dosing and administration; subject will take the Day -14 dose of study drug on-site
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring since the previous visit
- Record all concomitant medications that the subject has taken since the previous visit

6.5.3. Treatment Assessments for Cohorts 12-13

6.5.3.1. Day 1 Visit

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

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

- Symptom driven physical examination

- Record vital signs CCI [redacted]
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - ApoA1, ApoB
  - NMR Lipoprofile
  - Hemoglobin A1c
  - CCI [redacted]
  - Genomic sample
- Obtain urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Verify that study drug was taken correctly every day (Vascepa® [Cohort 12] or fenofibrate [Cohort 13] only)
- Dispense GS-0976 and GS-9674 and provide subject with dosing instruction on appropriate dosing and administration; subject will take the Day 1 dose of study drugs on-site
- Dispense Vascepa® (Cohort 12)
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events related to protocol mandated procedures since the previous visit

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

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning. All subjects should also be instructed **to hold** their dose of study drug on the morning of the visit until all fasting visit procedures have been completed and take their study drug(s) as instructed during the visit.

The following assessments will be performed and documented at the Day 28 (Week 4) Visit:

- Symptom driven physical examination
- Record vital signs CCI [redacted]

- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - NMR Lipoprofile
  - ApoA1, ApoB
  - CCI [redacted]
  - CCI [redacted]
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only
- Verify that study drug was taken correctly every day
- Dispense GS-9674 and GS-0976
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.5.3.3. Day 42 (Week 6) Visit (± 3 days)

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

The following assessments will be performed and documented at the Day 42 (Week 6) Visit:

- Symptom driven physical examination
- Conduct standard 12-Lead ECG
- Record vital signs CCI [redacted]
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - NMR Lipoprofile
  - ApoA1, ApoB

- CCI
- CCI

- Obtain Urine Samples for:
  - Urine pregnancy test for females of childbearing potential only
- Provide females of childbearing potential with urine pregnancy test to be completed on the day of the Phone Follow-Up Visit
- Verify that study drug was taken correctly every day
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.5.3.4. Early Termination (ET) Visit

Subjects should be instructed to fast (no food or drink, except water) on the evening prior to the visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

The following assessments will be performed and documented the ET Visit:

- Symptom driven physical examination
- Record vital signs, CCI
- Conduct standard 12-Lead ECG
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel
  - NMR Lipoprofile
  - ApoA1, ApoB
  - CCI
  - CCI
- Collect urine samples for:
  - Urine pregnancy test for females of childbearing potential only

- Provide females of childbearing potential with urine pregnancy test to be completed on the day of the ET Phone Follow-Up Visit
- Verify that study drug was taken correctly every day
- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit

6.5.3.5. Unscheduled Visits

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

At a minimum, the following assessments will be performed and documented:

- 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
- Obtain blood samples for:
  - Chemistry and hematology
  - Coagulation panel

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

6.5.4. Posttreatment Assessments for Cohorts 12-13

6.5.4.1. Day 56 (Week 8) Phone Follow-Up Visit (± 5 days)

A Phone Follow-Up Visit will be conducted 2 weeks after the Day 42 (Week 6) Visit.

The following assessments will be performed and documented at the Phone Follow-Up Visit:

- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit
- Record results from home urine pregnancy test for females of childbearing potential only. Note: home urine pregnancy test should be provided to the subject at the Day 42 (Week 6) Visit

6.5.4.2. Early Termination (ET) Phone Follow-Up Visit

For subjects who prematurely discontinue the study, an ET Phone Follow-Up Visit will be conducted 2 weeks after the date of the last dose of study drug.

The following assessments will be performed and documented at the ET Phone Follow-Up Visit:

- Record all concomitant medications that the subject has taken since the previous visit
- Record any serious adverse events and all adverse events since the previous visit
- Record results from home urine pregnancy test for females of childbearing potential only. Note: home urine pregnancy test should be provided to the subject at the Early Termination Visit

6.6. Assessments for Premature Discontinuation from Study

Subjects discontinuing prematurely from the study should have an ET Visit performed upon discontinuing. They should also have a Follow-Up Visit performed 4 weeks after the date of the last dose of study drugs (Cohorts 1-11); or a Phone Follow-Up Visit performed 2 weeks after the date of the last dose of study drugs (Cohorts 12-13). When medically feasible, the medical monitor must be consulted prior to subject discontinuation. The subject will be considered off-study after completion of these visits.

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

6.7. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Subject who develops a serious adverse event consisting of a serious hypersensitivity reaction
- 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 (see Section 7.5).
- 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 IRB/IEC

6.8. Description of Assessments

6.8.1. Clinical Laboratory Analytes

Chemistry:

CCI albumin, CCI bicarbonate, blood urea nitrogen (BUN),) creatine kinase (CPK) (Cohorts 10 and 11), Creatinine Clearance , calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total and CCI, total protein, uric acid, CCI C-peptide testing, lipid panel, insulin, pro-insulin, free fatty acids, lactate, and leptin.

Hematology:

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

HIV-1, HBV & HCV (Reflex to HCV RNA) serology, CCI urine drug screen (for amphetamines, cocaine, methadone, opiates), HbA1c, lipidomics, genomic sample collection, NMR lipoprofile, ApoA1, ApoB, beta-hydroxybutyrate, serum fructosamine, adiponectin, hsCRP, total bile acids, CCI

Biomarker Tests:

Kinetic Biomarker assessments, CCI CCI CCI

6.8.2. 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.

CCI [redacted]

CCI [redacted]

6.8.5. Medical History

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

6.8.6. Physical Examination

A complete physical examination must include source documentation of general appearance, and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; neurological. Height, vital signs, CCI [redacted] will also be collected.

6.8.7. Vital Signs

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

Blood pressure will be measured using the following standardized process:

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

6.8.8. Pregnancy Testing

All females of childbearing potential must have a negative serum pregnancy test at Screening. CCI [redacted] For Cohorts 1-11, urine pregnancy testing will occur at Day 1 (prior to dosing), every 4 weeks during the dosing period, and at 30 days following the last dose of study drug. For Cohorts 12-13, urine pregnancy testing will occur at Day-14, Day 1 (prior to dosing), Week 4, Week 6, and at two weeks following the last dose of study drug. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drug immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

6.8.9. Quality of Life (QoL) Measures

The Chronic Liver Disease Questionnaire (CLDQ), SF-36 Health Survey, and Work Productivity and Activity Impairment Questionnaire (WPAI) will be collected at Day 1 and Week 12 visits (Cohorts 1-11) and Week 24 (Cohorts 10-11). It is recommended to administer these questionnaires prior to the clinical and laboratory assessments. The subject should read the questionnaires by himself/herself and record the answers by himself/herself.

6.8.10. Child-Pugh-Turcotte Score

For Cohorts 7-8 and 12-13, the CPT score will be calculated from the central laboratory values attained at the Screening Visit. Assessment of ascites and hepatic encephalopathy will be determined by the site at the Screening Visit, as in Appendix 4 and will be entered into the eCRF. Records of concomitant medications for ascites and hepatic encephalopathy will be collected in the eCRF.

For Cohorts 10 and 11, the sites will calculate CPT scores per Appendix 4 from the central laboratory values and assessments of ascites and hepatic encephalopathy attained at visits outlined in Appendix Table 2. Records of concomitant medications for ascites and hepatic encephalopathy will be collected in the eCRF.

6.8.11. Creatinine Clearance

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

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

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

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

CCI [redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs may also include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure, overdose, or drug abuse/misuse reports.
- Any pre-existing condition that increases in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.
- Complications of pregnancy and non-elective termination of pregnancy (See Section 7.6.2.1)

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason

7.1.2. Serious Adverse Events

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

- Death
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules.

  Examples of medically important events include:

  - intensive treatment in an emergency room or at home for allergic bronchospasm
  - blood dyscrasias or convulsions that do not result in hospitalization
  - development of drug dependency or drug abuse

For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

<u>Clarification on Serious Adverse Events</u>

- Death is an outcome of an AE, and not an adverse event in itself.
- An SAE may occur even if the subject was not on investigational medicinal product at the occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. For example, an AE that is potentially life-threatening but not an immediate risk of death may be graded with the severity of Grade 4 and not be a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above.

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub investigator is responsible for assessing the relationship to IMP therapy using clinical judgment describing the event as either unrelated (No) or related (Yes) consistent with the following definitions:

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

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

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

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

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

7.2.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 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_5x7.pdf.

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 Reporting Requirements and Instructions for Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

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

Adverse Events

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

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

Serious Adverse Events

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

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported. Investigators are not obligated to actively seek SAEs after the protocol defined follow-up period however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

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

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 Sciences PVE:	Fax:	PPD
	Email:	PPD

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

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

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

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

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

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or 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 investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB 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

7.5.1. Observation for Drug Induced Liver Injury (DILI): (Cohorts 1-9)

At baseline, some subjects may have liver biochemistry levels above the upper limit of normal (ULN).

For subjects with CCI [redacted], close observation for DILI (as described below) should be considered in subjects with any of the following criteria (all labs confirmed by repeat testing):

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

- 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 CCI 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):

- CCI
- [redacted]
- CCI
- 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 (CCI, CCI, 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 drug has been discontinued and subject is asymptomatic

During a period of close observation, study drug can be continued, if desired, at the discretion of the Gilead Medical Monitor and the principal investigator during the DILI evaluation.

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

- [redacted]
- [redacted]
- [redacted]
- [redacted]

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 CCI 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 CCI)

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.

7.5.2. Observation for Drug Induced Liver Injury (DILI) (Cohorts 10-13)

At baseline, some subjects may have liver biochemistry levels above the ULN. Baseline values for liver tests CCI and total CCI will be determined by averaging the values obtained between and including Screening and Day 1. Please refer to the Covance Laboratory Manual or individual subject Covance laboratory report for gender and age specific reference ranges.

On-treatment elevations of CCI should be confirmed with repeat testing within 48-72 hours of results. If confirmed, and if no other cause of the laboratory abnormalities is immediately apparent, notify the Medical Monitor.

Subjects with CCI elevations as per Figure 7-1 must be placed into close observation (as described below).

- Obtaining a more detailed history of symptoms and prior or concurrent disease
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtaining a history of exposure to environmental chemical agents
- Ruling out other causes of liver disease as needed (obtain viral hepatitis panel, imaging for evaluation of biliary tract disease, etc. if required in the opinion of the Investigator)

- Continue to monitor liver biochemistries at least twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study drugs have been discontinued and the subject is asymptomatic

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

CCI

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

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

Other than in the case of the liver enzymes noted above, Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days of receipt of the original test results. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

7.5.3. CPT Score (Cohorts 10-11)

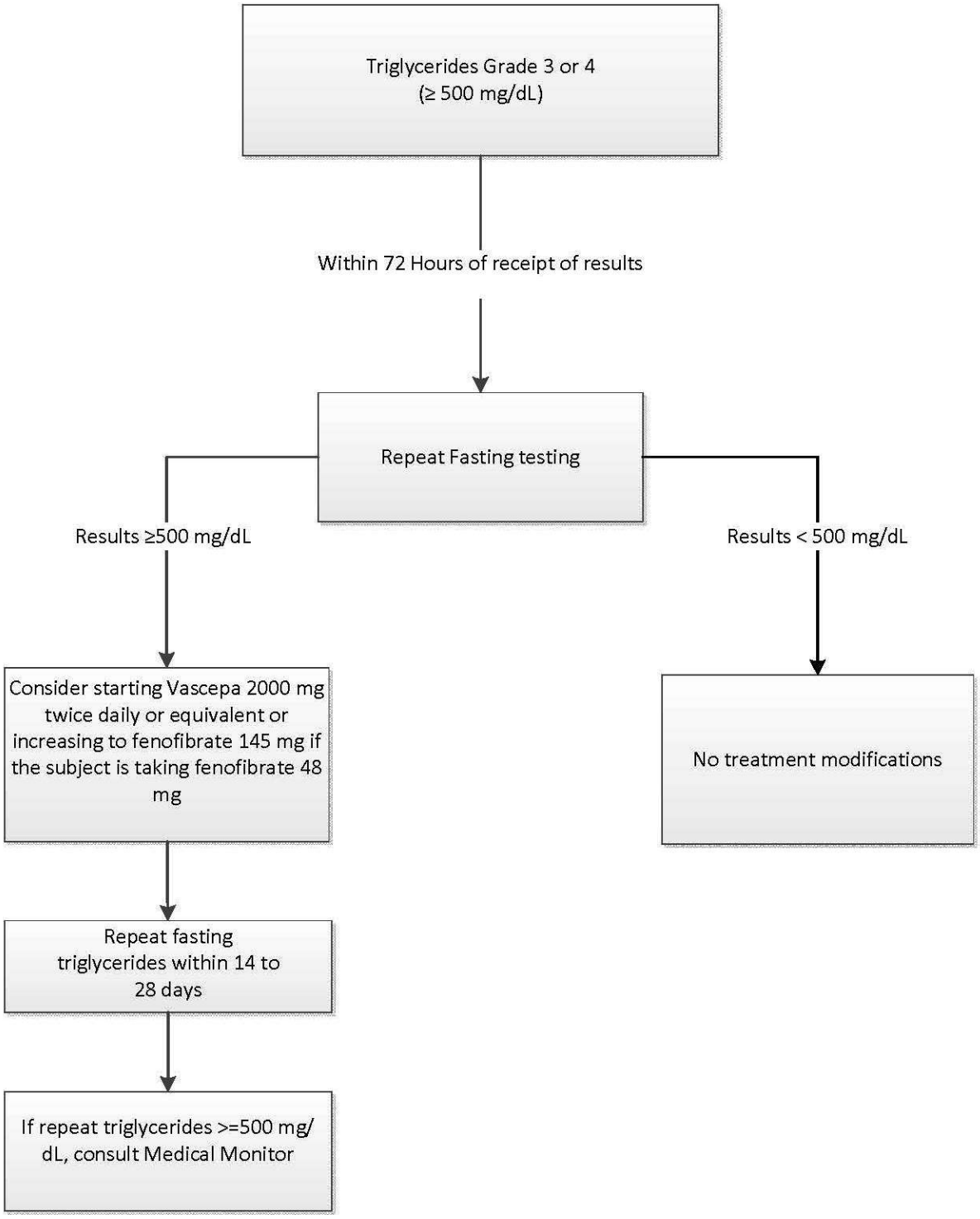
If a subject in Cohorts 10 or 11 has an increase in their CPT score to ≥ 7, this should be confirmed with repeat testing within 72 hours of receipt of results. If confirmed, the Medical Monitor should be notified and the subject should be placed in close observation, unless an alternate etiology (e.g., therapeutic anticoagulation) is identified. If the CPT score remains ≥ 7 for 2 consecutive weeks, and an alternate etiology has not been identified, study drugs must be discontinued.

7.5.4. Hypertriglyceridemia

7.5.4.1. Cohorts 10-11:

All subjects in Cohorts 10 and 11 will have baseline dyslipidemia. Figure 7-3 describes the recommended monitoring and intervention strategy for subjects that meet the criteria for treatment-emergent (on GS-0976 + fenofibrate) hypertriglyceridemia of Grade 3 or 4 (≥ 500 mg/dL).

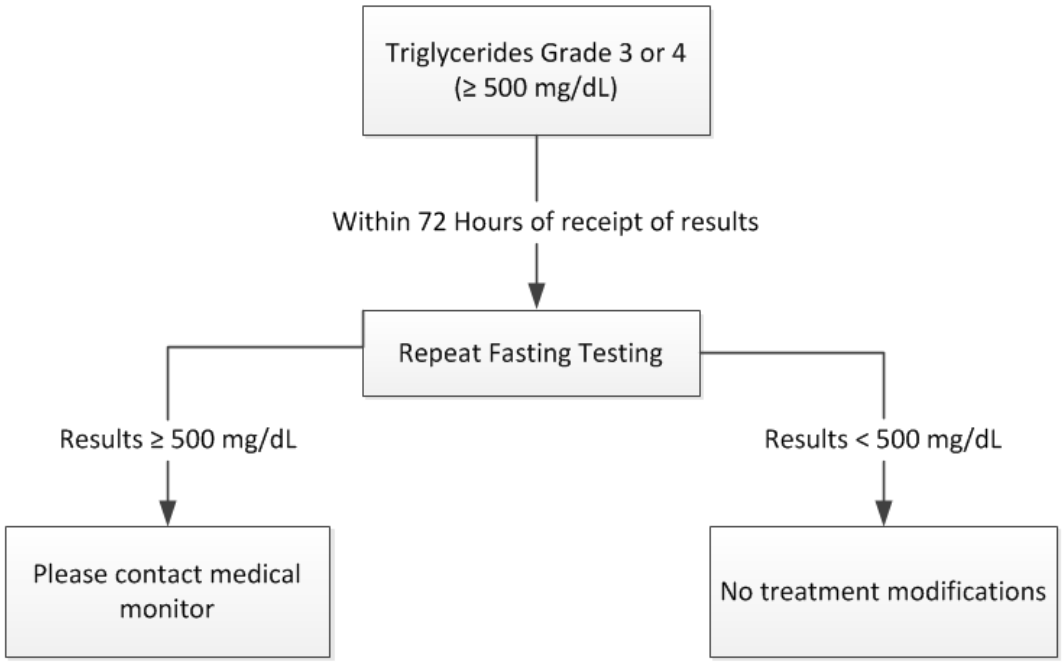
Figure 7-3. Algorithm for Monitoring and Treatment of Hypertriglyceridemia for Cohorts 10-11



7.5.4.2. Cohorts 12-13:

All subjects in Cohorts 12 and 13 will have baseline dyslipidemia. Figure 7-4 describes the recommended monitoring and intervention strategy for subjects that meet the criteria for treatment-emergent (on GS-0976 + GS-9674 + Vascepa® or fenofibrate) hypertriglyceridemia of Grade 3 or 4 (≥ 500 mg/dL).

Figure 7-4. Algorithm for Monitoring and Treatment of Hypertriglyceridemia for Cohorts 12-13



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, and pregnancy reports regardless of an associated AE.

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.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

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

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

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

7.6.2.2. Reporting Other Special Situations

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

Special situations involving non-Gilead concomitant medications 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 study drug(s) in subjects with NAFLD/NASH.

CCI [redacted]

8.1.2. Primary Endpoint

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

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

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

8.2.1.2. Safety

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

For Cohorts 10-13, a pretreatment safety analysis set will be defined and used to analyze the safety data during the pretreatment phase. This analysis set will include all subjects who received at least one dose of Vascepa® or fenofibrate. Subjects who received study drug other than that to which they were assigned will be analyzed according to the study drug received.

CCI [redacted]

8.2.1.4. Biomarkers

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

8.2.2. Interim Analysis

Administrative interim analyses may be performed to support safety review, for conferences and publications, or for regulatory interaction.

For Cohorts 1 to 9, administrative interim analyses will include data from the completed cohorts as well as the other ongoing cohorts. A formal interim analysis will be performed after the first 9 cohorts complete or early discontinue the study.

For Cohorts 10 and 11, an administrative interim analysis will be performed after all subjects complete 12 weeks of treatment or early discontinue treatment. A final analysis for these two cohorts will be performed after both cohorts complete or early discontinue the study.

For Cohorts 12 and 13, an administrative interim analysis may be performed for regulatory interaction or for conferences. A final analysis for these two cohorts will be performed after both cohorts complete or early discontinue the study.

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

8.4. Demographic Data and Baseline Characteristics

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

Baseline characteristics summary will include CCI [redacted], height, body mass index, presence or absence of diabetes, and other disease characteristic variables.

8.5. Efficacy Analysis

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

CCI [redacted]

[redacted]

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements, at various time points during the study, and by the documentation of AEs.

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

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the 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.

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.

The incidence of treatment-emergent laboratory abnormalities will be summarized by treatment group. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent.

8.6.4. Other Safety Evaluations

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

CCI [redacted]

[redacted]

8.8. Pharmacodynamic CCI [redacted] Analysis

8.8.1. Kinetic Biomarker Analysis

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

CCI [redacted]

[redacted]

8.9. Sample Size

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size in Cohorts 1 to 9. The number of subjects was chosen based on clinical experience with other similar proof of concept studies.

In Cohorts 10 and 11, we assumed that among subjects with baseline hypertriglyceridemia ≥150 mg/dL (60% with serum triglycerides ≥ 150 mg/dL and < 250 mg/dL and 40% with serum triglycerides ≥ 250 mg/dL and < 500 mg/dL) thus grade 3-4 hypertriglyceridemia (>500 mg/dL) would be observed in 28% following treatment with GS-0976. Assuming that the co-administration of fenofibrate and GS-0976 will reduce the incidence of Grade 3-4 hypertriglyceridemia to <5%, a sample size of 15 in each of Cohorts 10 and 11 will provide 82% power to detect the reduction based on a one-sided exact test at a significance level of 0.05.

In Cohorts 12 and 13, we assumed that among subjects with baseline hypertriglyceridemia (serum triglycerides ≥ 150 mg/dL and < 500 mg/dL), GS-0976 20 mg + GS-9764 30 mg once daily treatment will lead to a mean increase in serum triglycerides of 60 mg/dL from baseline after 6 weeks of treatment. Assuming that the co-administration of Vascepa® or fenofibrate with GS-0976 20 mg + GS-9764 30 mg will mitigate this increase in serum triglycerides and that the standard deviation for serum triglycerides after 6 weeks of treatment is 120 mg/dL, a sample size of 30 subjects in each cohort will provide 85% power to detect any increase based on a one-sided t-test at a significance level of 0.05.

8.10. Data Monitoring Committee

An internal Gilead data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data for Cohorts 1 through 9, due to the sequential enrollment design. The DMC will review cumulative data from these cohorts. The DMC will be notified of any case of suspected DILI by the medical monitor. The DMC will provide recommendations whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

There will be no formal DMC review for Cohorts 10-13. However, internal safety monitoring will be conducted continuously on an ongoing basis.

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. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

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

The investigator and all applicable sub investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub investigator's) participation in the study. The investigator and sub investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

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

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

9.1.3. Informed Consent

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

[redacted]

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC 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 for further details. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

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

9.1.5. Study Files and Retention of Records

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

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

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

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

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

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

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

9.1.6. Electronic Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed in a timely manner to enable the sponsor to perform central monitoring of safety data. 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. At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Gilead and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure of investigational medicinal product/destruction in order to ensure that it complies with Gilead requirements. Drug may be returned or destroyed on an ongoing basis during the study, if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet Gilead's requirements for disposal, arrangements will be made between the site and Gilead or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

9.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences and its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead Sciences. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency (ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from Gilead Sciences, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media **only after the following conditions have been met:**

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form; o
- The study has been completed at all study sites for at least 2 years

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

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Monitoring and Oversight of Biomarker Specimens

Biomarker research specimens will be tracked in a manner consistent with Good Clinical Practice (GCP) 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 authorities, IRBs, IECs, and ECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

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

GS-US-384-3914, Amendment 12, 11 September 2019

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

PPD

Signature

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Tables for GS-US-384-3914

Appendix Table 1. (Cohorts 1-9)

		Pretreatment Period		Enrollment		Treatment Period							End of Treatment					Follow Up
		Kinetic Biomarkers Cycle 1					Kinetic Biomarkers Cycle 2						Kinetic Biomarkers Cycle 3					
	Screen[a]	Day -14	Day -11 (±1d)	Day -7 (±1d)	Day 1[b]	Day 7 (WK1) (±3d)	Day 14 (WK2) (±1d)	Day 17 (±1d)	Day 21 (WK3) (±1d)	Day 28 (WK4) (±3d)	Day 35 (WK5) (±3d)	Day 56 (WK8) (±3d)	Day 70 (WK10) (±1d)	Day 73 (±1d)	Day 77 (WK11) (±1d)	Day 84 (WK12) (±3d)	Day 91 (WK13) (±3d)	Day 112 (WK16) (±5d)
Clinical Assessments																		
Informed Consent	X																	
Determine Eligibility[c]	X	X			X													
Medical History	X				X													
Assess ascites and hepatic encephalopathy[d]	X																	
Physical Examination	X				X[e]	X[e]				X[e]		X[e]				X[e]		X[e]
Vital Signs	X				X	X				X		X				X		X
Height	X																	
CCI																		
12-lead ECG	X															X		
QoLs[f]					X											X		
CCI																		
Adverse Events	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X
Dispense Study Drug					X					X		X						
Dispense Deuterated Water		X					X						X					

		Pretreatment Period		Enrollment		Treatment Period										End of Treatment		Follow Up
		Kinetic Biomarkers Cycle 1					Kinetic Biomarkers Cycle 2						Kinetic Biomarkers Cycle 3					
	Screen[a]	Day -14	Day -11 (±1d)	Day -7 (±1d)	Day 1[b]	Day 7 (WK1) (±3d)	Day 14 (WK2) (±1d)	Day 17 (±1d)	Day 21 (WK3) (±1d)	Day 28 (WK4) (±3d)	Day 35 (WK5) (±3d)	Day 56 (WK8) (±3d)	Day 70 (WK10) (±1d)	Day 73 (±1d)	Day 77 (WK11) (±1d)	Day 84 (WK12) (±3d)	Day 91 (WK13) (±3d)	Day 112 (WK16) (±5d)
Laboratory Assessments																		
Chemistry	X				X	X				X		X				X		X
Hematology	X				X	X				X		X				X		X
Coagulation Panel	X				X	X				X		X				X		X
Pregnancy Test[h]	X				X					X		X				X		X
ApoA1, ApoB, Total bile acids, NMR Lipoprofile					X	X				X		X				X		
Phospho-p38[i], adiponectin, beta-hydroxybutyrate					X					X						X		
CCI																		
Lipidomics					X					X						X		
CCI																		
FGF19, C4					X	X				X		X				X		
CCI																		
Hemoglobin A1c					X											X		
Urine Drug Screening	X																	
HIV-1, HBV & HCV Serology	X																	
CCI																		
Stool Collection					X[k]											X[k]		
Genomic Sample[l]					X													

	Screen[a]	Pretreatment Period				Enrollment	Treatment Period										End of Treatment		Follow Up
		Kinetic Biomarkers Cycle 1					Kinetic Biomarkers Cycle 2						Kinetic Biomarkers Cycle 3						
		Day -14	Day -11 (±1d)	Day -7 (±1d)	Day 1[b]	Day 7 (WK1) (±3d)	Day 14 (WK2) (±1d)	Day 17 (±1d)	Day 21 (WK3) (±1d)	Day 28 (WK4) (±3d)	Day 35 (WK5) (±3d)	Day 56 (WK8) (±3d)	Day 70 (WK10) (±1d)	Day 73 (±1d)	Day 77 (WK11) (±1d)	Day 84 (WK12) (±3d)	Day 91 (WK13) (±3d)	Day 112 (WK16) (±5d)
CCI																			
Urine Collection for Kinetic Biomarkers		X	X	X	X	X[m]	X	X	X	X		X[m]	X	X	X	X		
Blood Collection for Kinetic Biomarkers		X	X	X	X	X[m]	X	X	X	X		X[m]	X	X	X	X		
Saliva Collection for Kinetic Biomarkers[n]						X					X[k]						X[k]	

a Screening assessments to be completed within 6 weeks prior to Day -14 visit. The screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences.
b Day 1 assessments must be performed prior to dosing.
c Includes review of historical liver biopsy, obtained within 12 months of Screening (date of initial informed consent) for subjects with bridging fibrosis (F3) and within the last 12 months for subjects with cirrhosis (F4), to assess subject eligibility.
d Assess presence and severity of ascites and hepatic encephalopathy for CPT score (for Cohorts 7 and 8 only).
e Symptom driven physical examination.
f For subjects with Quality of Life questionnaires available at Day 1.
CCI [redacted]
h Females of childbearing potential only: Serum pregnancy testing at screening, urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period and for 30 days following the last dose of study drug.
i Phospho-p38 will be collected if reagent is available.
CCI [redacted]
k To be collected at home and provided to the site at the next visit.
l Genomic Sample collected for subjects who have not opted out of sample collection. No additional blood will be drawn.
m Predose Kinetic Biomarkers (for Cohorts 4-9) and 2 hour (± 1 hour) postdose Kinetic Biomarkers (for Cohorts 5, 6, 7 and 9).
n Saliva Collection for Kinetic Biomarkers to be collected for Cohorts 1-3 only.

Appendix Table 2. (Cohorts 10-11)

		Pretreatment Period / Enrollment				Treatment Period													EOT	ET	FU
		Kinetic Biomarkers Cycle 1							Kinetic Biomarker Cycle 2						Kinetic Biomarker Cycle 3						
	Screen[a]	D -14	D -11 (±1d)	D -7 (±1d)	D1[b]	D7 (W1) (±3d)	D28 (W4) (±3d)	D56 (W8) (±3d)	D70 (W10) (±1d)	D73 (±1d)	D77 (W11) (±1d)	D84 (W12) (±3d)	D112 (W16) (±3d)	D126 (W18) (±3d)	D154 (W22) (±1d)	D157 (±1d)	D161 (W23) (±1d)	D168 (W24) (±3d)	ET	D196 (W28) (±5d)
Clinical Assessment																				
Informed Consent	X																			
Determine Eligibility[c]	X	X																		
Medical History	X	X			X															
Assess ascites and hepatic encephalopathy	X				X	X	X	X				X	X					X	X	
CPT score	X				X	X	X	X				X	X					X	X	
Physical Examination	X	X[d]			X[d]	X[d]	X[d]	X[d]				X[d]	X[d]					X[d]	X[d]	X[d]
Vital Signs	X	X			X	X	X	X				X	X					X	X	X
Height	X																			
CCI																				
12-lead ECG	X											X						X	X	
QoLs[e]					X							X						X	X	
CCI																				
CCI																				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense fenofibrate		X						X						X						
Dispense GS-0976					X		X	X				X	X	X						

		Pretreatment Period / Enrollment				Treatment Period													EOT	ET	FU
		Kinetic Biomarkers Cycle 1							Kinetic Biomarker Cycle 2						Kinetic Biomarker Cycle 3						
	Screen[a]	D-14	D-11 (±1d)	D-7 (±1d)	D1[b]	D7 (W1) (±3d)	D28 (W4) (±3d)	D56 (W8) (±3d)	D70 (W10) (±1d)	D73 (±1d)	D77 (W11) (±1d)	D84 (W12) (±3d)	D112 (W16) (±3d)	D126 (W18) (±3d)	D154 (W22) (±1d)	D157 (±1d)	D161 (W23) (±1d)	D168 (W24) (±3d)	ET	D196 (W28) (±5d)
Dispense Deuterated Water		X[k]							X						X					
Laboratory Assessments																				
Chemistry	X	X	X	X	X	X	X	X				X	X					X	X	X
Hematology	X	X	X	X	X	X	X	X				X	X					X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X				X	X					X	X	X
Pregnancy Test[h]	X				X		X	X				X	X		X			X	X	X
Adiponectin, beta-hydroxybutyrate		X			X							X						X	X	
hsCRP		X			X							X						X	X	
ApoA1, ApoB, Total bile acids, NMR Lipoprofile		X			X	X	X	X				X	X					X	X	
CCI																				
Lipidomics		X			X	X	X	X				X	X					X		
CCI																				
CCI																				
Hemoglobin A1c	X	X			X							X						X	X	
Urine Drug Screening	X																			
HIV-1, HBV & HCV Serology	X																			

		Pretreatment Period / Enrollment				Treatment Period													EOT	ET	FU
		Kinetic Biomarkers Cycle 1							Kinetic Biomarker Cycle 2						Kinetic Biomarker Cycle 3						
	Screen[a]	D -14	D -11 (±1d)	D -7 (±1d)	D1[b]	D7 (W1) (±3d)	D28 (W4) (±3d)	D56 (W8) (±3d)	D70 (W10) (±1d)	D73 (±1d)	D77 (W11) (±1d)	D84 (W12) (±3d)	D112 (W16) (±3d)	D126 (W18) (±3d)	D154 (W22) (±1d)	D157 (±1d)	D161 (W23) (±1d)	D168 (W24) (±3d)	ET	D196 (W28) (±5d)
CCI																				
CCI																				
Genomic Sample[j]					X															
CCI																				
Urine Collection for Kinetic Biomarkers		X	X	X	X	X[m]		X[m]	X	X	X	X		X	X	X	X	X	X	
Blood Collection for Kinetic Biomarkers		X	X	X	X	X[m]		X[m]	X	X	X	X		X	X	X	X	X	X	
CCI																				

a Screening assessments to be completed within 6 weeks prior to Day -14 visit. The screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences.
b Day 1 assessments must be performed prior to dosing.
c Includes Review of historical liver biopsy obtained within the last 6 months of Screening (date of initial informed consent) for subjects with bridging fibrosis (F3) and within the last 12 months for subjects with cirrhosis (F4), to assess subject eligibility
d Symptom driven physical examination.
e For subjects with Quality of Life questionnaires available at Day 1.
CCI
CCI
h Females of childbearing potential only: Serum pregnancy testing at screening, urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period and for 30 days following the last dose of study drug.
CCI
j Genomic Sample collected for subjects who have not opted out of sample collection. No additional blood will be drawn.
k The first dose of 50 mL deuterated water will be administered under the supervision of investigative site personnel and monitored for at least 30 minutes after for any side effects.
CCI
m Predose Kinetic Biomarkers and 2 hour (± 1 hour) postdose Kinetic Biomarkers.

Appendix Table 3. (Cohorts 12-13)

	Screen[a]	Pretreatment Period/ Enrolment	Treatment Period		End of Treatment	ET	Phone Follow-Up	ET Phone Follow-Up
		D 14	D1[b]	D28 (W4) (±3d)	42 (W6) (±3d)	ET	56 (W8) (±5d)	2 Weeks After Last Dose
Clinical Assessment								
Informed Consent	X							
Determine Eligibility[c]	X	X						
Medical History	X	X						
Assess Ascites and Hepatic Encephalopathy	X							
CPT Score	X							
Physical Examination	X	X[d]	X[d]	X[d]	X[d]	X[d]		
Vital Signs	X	X	X	X	X	X		
Height	X							
CCI								
12-lead ECG	X				X	X		
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Dispense Vascepa® (Cohort 12)		X	X					
Dispense Fenofibrate (Cohort 13)		X						
Dispense GS-0976 and GS-9674			X	X				
Review of Study Drug Dosing Compliance (Pill Count)			X[e]	X	X			
Chemistry	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X		
Coagulation Panel	X	X	X	X	X	X		
Pregnancy Test[f]	X	X	X	X	X	X	X	X
CCI								
ApoA1, ApoB, NMR Lipoprofile		X	X	X	X	X		
CCI								

	Screen[a]	Pretreatment Period/ Enrollment	Treatment Period		End of Treatment	ET	Phone Follow-Up	ET Phone Follow-Up
		D-14	D1[b]	D28 (W4) (±3d)	D42 (W6) (±3d)	ET	D56 (W8) (±5d)	2 Weeks After Last Dose
Hemoglobin A1c	X		X					
Urine Drug Screening	X							
HIV-1, HBV & HCV Serology	X							
Genomic Sample[j]			X					
CCI								

a Screening assessments to be completed within 4 weeks prior to Day -14 visit. The screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences.
b Day 1 assessments must be performed prior to dosing.
c Includes review of historical liver biopsy obtained within 6 months of the Screening Visit for subjects without compensated cirrhosis (F4) or within 12 months of the Screening Visit for subjects with compensated cirrhosis (F4); or review of historical MRE or historical FibroScan® obtained within 6 months of the Screening Visit.
d Symptom driven physical examination.
e Vascepa® (Cohort 12) or fenofibrate (Cohort 13) only
f Females of childbearing potential only: Serum pregnancy testing at screening, urine pregnancy testing will occur at D-14, D1, D28, D42, and 2 weeks after last dose of study drug. Home urine pregnancy test for Phone Follow-Up will be provided at the D42 Visit or ET Visit.
[redacted]
j Genomic Sample collected for subjects who have not opted out of sample collection. No additional blood will be drawn.

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

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following menarche until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

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

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

b) Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

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

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

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

Preclinical data in human hepatocytes indicate that GS-0976 is a mild inducer of CYP3A4 isoenzymes. Clinical data demonstrates no decrease in exposure of a representative oral hormonal contraceptive indicating no loss of contraceptive efficacy is expected upon administration of GS-0976 with hormonal contraceptives. Please refer to the latest version of the GS-0976 Investigator's Brochure for additional information.

GS-9674 has not yet been studied in pregnant women. In initial dose range-finding studies in pregnant mice and rabbits there were no effects on embryofetal development other than a decrease in fetal body weights in the pregnant rabbits administered 1000 mg/kg/day. The decrease in fetal body weights are likely secondary to maternal toxicity rather than a direct effect of GS-9674. The NOEL for embryo/fetal development is 300 mg/kg/day in mice and 200 mg/kg/day in rabbits. These doses were associated with exposures that are > 50-fold higher than the anticipated human exposure at the maximum proposed human dose of 100 mg once daily.

Drug-drug interaction (DDI) data do not suggest a potential for interaction between GS-9674 and hormones used for contraception. Please refer to the latest version of the GS-9674 Investigator's Brochure for additional information.

Please see fenofibrate label for further information regarding fenofibrate and pregnancy.

Please see Vascepa® label for further information regarding Vascepa® and pregnancy.

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. All females of childbearing potential must have a negative serum pregnancy test at Screening. Cohorts 1-11 must have a negative pregnancy test on the Baseline/Day 1 visit prior to enrollment. Pregnancy tests will be performed at monthly intervals thereafter. For Cohorts 12-13, urine pregnancy testing will occur at Day-14, Day 1 (prior to dosing), Week 4, Week 6, and at two weeks following the last dose of study drug.

Female subjects must agree to one of the following from Screening until 90 days following the last dose of study drug.

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

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Tubal sterilization

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

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

- Should female subjects wish to use a hormonally based method, use of a male condom by the female subject's male partner is required. Subjects who utilize a hormonal contraceptive as one of their birth control methods must have used the same method for at least three months prior to study dosing. Hormonally-based contraceptives permitted for use in this protocol are as follows:
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 90 days after the last dose of study drug.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject’s seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until 90 days after the last dose of study drug. Female partners of male study subjects are asked to select one of the above methods.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the last dose of study drug.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 90 days of last study drug dose. Subjects who

become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 4. Child-Pugh-Turcotte Classification of the Severity of Cirrhosis

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

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