A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 3-ARM, PARALLEL- GROUP STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACODYNAMICS OF PF-06835919 ADMINISTERED ONCE DAILY FOR 6 WEEKS IN ADULTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Investigational Product (IP) Number:	PF-06835919
IP Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	131743
European Clinical Trials Database (EudraCT) Number:	2016-004649-10
Protocol Number:	C1061003
Phase:	2a

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	29 June 2017	N/A

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

SCHEDULE OF ACTIVITIES

The schedule of activities table below provides an overview of the protocol visits and procedures. Refer to Section 6 and 7 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier [for abbreviations, refer to Appendix 1]	**Screen 1**	**Screen 2**	**Run-In**	**Base-line**	**Treatment Phase[a]**				**Follow-up**		**Early Termination**
Week Relative to Dosing on Day 1			**-2**	**-1**	**0**	**2**	**4**	**6**	**7-8**	**10-11[b]**	
Days Relative to Dosing on Day 1			**-14±2**	**-4±2**	**1**	**14±2**	**28±2**	**40±2**	**--**	**--**	
Visit to Site	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	
Informed consent & demography	X										
Medical & medication history (update)	X		X		X	X	X	X	X	X	X
Liver fat and stiffness (via FibroScan®)	X				X	X	X	X	X		X
Liver fat (via MRI-PDFF)		X		X				X[c]			
Physical examination[d]	X		X						X		X
Confirm contraceptive method	X		X		X	X	X	X	X	X	X
Serious & non-serious AE monitoring	X	→	X	→	X	X	X	X	X	X	X
Body weight	X		X		X	X	X	X	X		X
Supine 12-lead ECG	X		X		X	X	X	X	X		X
Seated vitals (BP & pulse rate)	X		X		X	X	X	X	X		X
Randomization in trial (via IRT)					X						
Dispense IP (via IRT)			X		X	X	X				
Witnessed dosing on site of IP			X		X	X	X	X			
Compliance via pill count of returned IP					X	X	X	X			X
Administration of IP			X	→	X	→	→	X			
Blood Collections after ≥8-hour fast											
Clinical laboratory tests	X		X		X	X	X	X	X		X
FSH (females), HepB, HepC, HIV, coagulation, α1-antitrypsin, ceruloplasmin	X										
CCI	■		■		■	■	■	■	■		■
■			■		■	■	■	■			■
■			■		■			■			■
■					■	■	■	■			■
■					■						
■					■			■			■
Urine Collections											
Urine drug test	X										
■ CC			■				■				
Urinalysis, including microscopy[f]	X		X		X	X	X	X	X		X

a. All procedures before morning dose of IP.
b. May occur via telephone contact and must occur 28-35 days from administration of the final dose of double-blind IP.
c. MRI-PDFF assessment to be performed within approximately 24 hours prior to the Visit 8, or on the same day as Visit 8
d. Includes arm and waist circumference, and height at Visit 1 only.
e. A blood sample for PK analysis will be collected prior to dosing at Visit 7. An additional PK sample will be collected the following day when subjects return to the site to complete the 24-hour urine collection, prior to dosing.
f. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.
g. Subjects to perform two 24-hour urine collections as outpatients: once during the 14-day Run-In and another within 24 hours of Visit 7 (Day 28).

1. INTRODUCTION

Ketohexokinase (KHK) is an enzyme catalyzing the conversion of fructose and adenosine triphosphate (ATP) to fructose-1-phosphate (F1P) and adenosine diphosphate (ADP), the first committed step in fructose metabolism. Loss of function mutation in KHK, known as Essential Fructosuria, is a rare autosomal genetic condition (Online Mendelian Inheritance in Man or OMIM #229800)[1] which is asymptomatic, and is only recognized by the appearance of fructose in the urine after fructose consumption.[2,3] PF-06835919 is a potent, reversible inhibitor of human KHK. It is anticipated that inhibition of KHK will decrease hepatic de novo lipogenesis and steatosis, thereby ameliorating the pathogenesis of nonalcoholic fatty liver disease (NAFLD) and its progression to nonalcoholic steatohepatitis (NASH). In addition, it is anticipated that KHK inhibition will improve circulating lipid and lipoprotein profiles as well as insulin sensitivity.

The purpose of this study is to assess safety and tolerability, as well as the effect of PF-06835919 on liver fat and additional pharmacodynamic (PD)/exploratory parameters in subjects with NAFLD.

1.1. Mechanism of Action/Indication

PF-06835919 is a KHK inhibitor that is currently being developed for the treatment of NAFLD/NASH.

1.2. Background

Fructose metabolism, unlike glucose metabolism, is not subject to regulatory feedback inhibition in normal human biology. As a consequence of unrestrained metabolism, fructose rapidly generates a number of reactive and signaling metabolites that contribute to metabolic disease progression. Along with the lack of feedback inhibition, hepatic fructose metabolism has been shown to reduce liver ATP concentrations after a single intravenous (IV) bolus of fructose.[4] Depletion of ATP leads to the activation of adenosine monophosphate (AMP) deaminase[5] and subsequent increases in uric acid levels that have been shown to directly regulate hepatic lipogenesis through generation of mitochondrial oxidative stress.[6] Additionally, preclinical studies have demonstrated that fructose rapidly enriches glycolytic metabolite pools, leading to activation of the Carbohydrate Response Element Binding Protein (ChREBP), a highly lipogenic transcription factor, that can promote both steatosis and insulin resistance with carbohydrate over-feeding.[7] Post-prandial hypertriglyceridemia is observed in both rodents and humans following fructose feeding, as fructose both decreases very low density lipoprotein (VLDL) clearance and promotes de novo lipogenesis.[8]

Excessive fructose consumption has been shown to cause features of metabolic syndrome and NAFLD.[8] In humans, supplementation of a normal diet with 25% of the calories as fructose, but not as glucose, caused hyperlipidemia within 2 weeks.[9] Additionally, these subjects developed insulin resistance as evidenced by increased insulin excursion during an oral glucose tolerance test.[9] Increased sugar intake, in the form of carbonated beverages, has been associated with NAFLD in patients who lack other features of metabolic syndrome, suggesting that fructose intake independent of metabolic disease can increase liver fat.[10,11] In

a separate study with subjects consuming weight-neutral diets containing 25% of dietary calories as fructose, increased hepatic lipid and decreased hepatic insulin sensitivity were observed after 9 days of high-fructose consumption.[12] Conversely, restricting dietary sugar intake from 28% to 10% for 9 days improved insulin sensitivity and reduced hepatic lipid in obese adolescents.[13] In a separate study, fructose at 5%, 8.75%, or 12.5% of the daily caloric intake showed a dose-responsive slight elevation in plasma triglycerides and elevation in uric acid.[14] In studies with matched calories provided as free glucose, fructose was unique in its ability to promote insulin resistance, visceral obesity and hyperlipidemia.[9] Collectively, these data suggest that the fructose, not glucose, component of dietary sugar is unique in its ability to promote features of metabolic syndrome, including steatosis, insulin resistance, and obesity.

NASH is a clinical and histological subset of NAFLD that is associated with increased all-cause mortality, cirrhosis and end-stage liver disease, increased cardiovascular mortality, and increased incidence of both liver-related and non-liver-related cancers.[15] Prevalence of NAFLD is estimated at 30-40% of the US population, while prevalence of NASH is estimated at 3-5% of US population.[15] Risk factors for NASH include obesity, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia, as manifested by low levels of high density lipoprotein cholesterol (HDL-C) and elevated triglycerides.

There are no therapies currently approved for the treatment of NASH, although a growing body of evidence demonstrates the urgent need for such therapies.[15] NASH is diagnosed clinically by liver biopsy demonstrating steatosis, inflammation, and cytological ballooning of hepatocytes, often with varying degrees of fibrosis. The clinical progression of NASH involves increasing degrees of fibrosis, with cirrhosis and/or hepatocellular carcinoma developing in a subset of patients.[15] Patients with NASH may be asymptomatic or have non-specific symptoms such as fatigue, despite having significant disease shown by liver biopsy. More severe NASH is associated with elevated risk for progression to cirrhosis and liver-related mortality.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure for PF-06835919. A summary of the information relevant to this study is presented below.

CCI [redacted]

CCI [redacted]

[redacted]

CCI

[redacted]

CCI [redacted]

1.2.2. Clinical Experience with PF-06835919

As of June 2017, the first in human (FIH) study C1061001 has been completed, and the ongoing multiple ascending dose study C1061002 completed 2 weeks of dosing in 5 cohorts of subjects. In addition, 12 subjects completed a drug-drug interaction assessment with atorvastatin, in which doses of 50 mg and 280 mg of PF-06835919 were each administered for 4 days (8 days of total dosing). A total of 78 healthy adult subjects (all males) have been randomized in these 2 studies. Overall, 68 subjects (87%) were exposed to at least a single oral dose of PF-06835919; with 52 of these subjects exposed to repeated doses of PF-06835919.

CCI

[redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

CCI

CCI

CCI

CCI

CCI [redacted]

CCI [redacted]

CCI [redacted]

1.3. Study Rationale

The current study is the first trial designed to evaluate the effect of 6 weeks of oral, once-daily, dosing of PF-06835919 on liver fat, and other PD/exploratory parameters in adults with NAFLD.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

1.3.2. Rationale for Population Enrolled

The patient population most likely to benefit from therapy with a KHK inhibitor (KHKi) is comprised of those who are obese, diabetic, and/or have metabolic syndrome. Therefore, the study population included in this study will be obese subjects (body mass index [BMI] ≥28 kg/m^2) with clinical indicators of metabolic syndrome and/or T2DM.

CCI

[redacted]

CCI

[redacted]

1.3.3. Dose Rationale

This study is planned as a 3-arm, parallel group study with 2 active PF-06835919 doses (75 mg once daily [QD] and 300 mg QD) and placebo to evaluate changes in liver fat.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

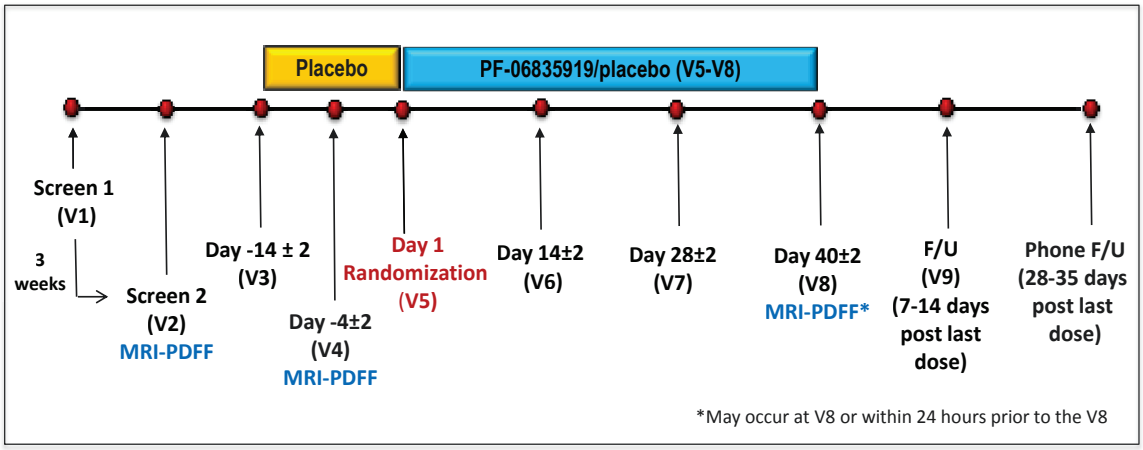
Primary Objective:	Primary Endpoint:
To evaluate the effect of daily administration of PF-06835919 over 6 weeks on liver fat in adults with NAFLD	Percent change from baseline in liver fat at Week 6, as assessed by MRI-PDFF
Secondary Objectives:	**Secondary Endpoints:**
To evaluate the safety and tolerability of PF-06835919 administered daily over 6 weeks to adults with NAFLD	Assessment of TEAEs, clinical laboratory tests, vital signs, and 12-lead ECGs
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

In all cases, baseline defined as result closest ***prior to*** dosing at Visit 5 (Day 1).

3. STUDY DESIGN

3.1. Study Overview

This will be a randomized, double-blind, stratified, placebo-controlled, 3-arm (placebo, plus



Determination of eligibility for this study will occur via a sequential, 2-step process, starting at the first screening visit (Screen 1). Subjects identified to be eligible based on Screen 1 procedures will proceed to Screen 2 to measure liver fat by MRI-PDFF.

Once confirmed to be eligible based on results of Screen 2, subjects will progress to a Run-in period (Visit 3), at which time subjects receive single-blind placebo for approximately 14 days to ensure compliance with the administration of IP. During the Run-in period, subjects will complete a 24-hour urine collection. In addition, approximately 4 days prior to randomization (Visit 4), subjects will report to the imaging center to have a baseline MRI-PDFF scan performed. At Visit 5 (Day 1), subjects will be randomized to receive 1 of 3 blinded IP regimens for a duration of approximately 6 weeks (ie, 40±2 days). A second 24-hour collection will be performed around Visit 7 (Day 28), which will require an additional visit to the study site.

This study includes a total of 9 scheduled outpatient visits to the study site, 3 visits to the imaging center, and a safety Follow-up telephone contact. The total participation, from Visit 1 (Screen 1) to the on-site Follow-up visit (Visit 9), will be up to approximately 11-14 weeks.

Up to 51 subjects (17 per arm) will be randomized at approximately 6-8 sites to ensure that a minimum of approximately 42 subjects (14 per arm) complete the study. The approximate 51 randomized subjects account for a projected premature withdrawal rate of 15%.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is

considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria

Subjects must meet **all** of the following inclusion criteria to be eligible for enrollment into the study:

1. Male subjects or female subjects of non-childbearing potential between the ages of 18 and 65 years, inclusive, at Visit 1 (Screen 1)

   - Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

     a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status should be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

     b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

     c. Have medically confirmed ovarian failure.

     All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

2. At Visit 1 (Screen 1), total body weight of >50 kg (110 lbs) and a BMI ≥28 kg/m^2;

3. At Visit 1 (Screen 1), a CAP™ ≥260 dB/m via FibroScan® assessment;

4. Subjects with a medical diagnosis of T2DM being treated with no more than 1 acceptable oral antidiabetic drug (see Section 5.8.1); **or** meeting **≥2** of the following criteria, as assessed by sponsor-identified central laboratory, with a single repeat on any of these parameters permitted to assess eligibility, if needed:

   a. Fasting plasma glucose ≥100 mg/dL;

   b. Fasting HDL-C <40 mg/dL for males and <50 mg/dL for females; or on pharmacological agents *with explicit purpose* to increase HDL-C (refer to Section 5.8.2 for acceptable versus prohibited medications;

c. Fasting triglycerides ≥150 mg/dL; or on pharmacological agents with explicit purpose to decrease triglycerides (refer to Section 5.8.2 for acceptable versus prohibited medications);

d. Seated systolic blood pressure (BP) within the range of 120-159 mmHg, inclusive; and seated diastolic BP within the range of 80-99 mmHg, inclusive; or on pharmacologic agents for blood pressure (BP) control (refer to Section 5.8.3);

e. Waist circumference ≥40 inches for males and ≥35 inches for females with a maximum that allows for a subject to fit comfortably within the MRI machine;

5. At Visit 2 (Screen 2), liver fat ≥6% measured by MRI-PDFF acquisition protocol at the Sponsor-qualified Imaging facility, confirmed via a single repeat, if deemed necessary by the Sponsor-identified central imaging vendor(refer to Section 7.6.2);

6. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study;

7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects currently experiencing any clinically significant or unstable medical condition that might limit their ability to complete the study, to comply with the requirements of the protocol, or interfere with the interpretation of study results which, in the judgment of the investigator, would make the subject inappropriate for entry into this study, including: dermatologic disease, hematological disease, pulmonary disease, hepatic disease, gastrointestinal disease, genitourinary disease, endocrine disease, neurological disease and psychiatric disease;

2. Subjects with any of the following clinical laboratory abnormalities at Visit 1 (Screen 1), as assessed by sponsor-identified central laboratory and confirmed by a single repeat, if deemed necessary:

   - Fasting triglycerides >500 mg/dL;
   - Fasting direct LDL-C >190 mg/dL;
   - AST, ALT, or gamma glutamyl transferase (GGT) >2.0 x upper limit of normal (ULN);
   - Hemoglobin A1c (HbA1C) >8.5%;

- Fasting plasma glucose >270 mg/dL;
- Total bilirubin >1.5x ULN **and** direct bilirubin ≥ULN;
- Albumin < lower limit of normal (LLN);
- International normalized ratio (INR) ≥1.3;

3. History of regular alcohol consumption exceeding 14 drinks/week for females **or** 21 drinks/week for males [1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor)] within the previous 6 months;

4. A positive urine drug test for illicit drugs at the Screen 1 (Visit 1). Subjects that have been medically prescribed opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at the screening visit may be allowed to participate if approved by the sponsor;

5. Seated systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg after ≥5 minutes of rest
   - If needed, BP may be repeated 2 more times and the average value of the 3 BP measurements will be used to assess eligibility;

6. Supine 12-lead ECG demonstrating QTc interval >450 msec **or** a QRS interval >120 msec
   - If QTc interval exceeds 450 msec, or QRS interval exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc intervals or QRS intervals should be used to determine the subject's eligibility;

7. Subjects with an estimated glomular filtration rate <30 mL/min as calculated by the modification of diet in renal disease equation (MDRD), and confirmed via a single repeat, if deemed necessary;

8. Evidence or diagnosis of other forms of chronic liver disease, including but not limited to the entities listed below; evidence may include laboratory tests, as assessed by the Sponsor-identified central laboratory, with a single repeat at Visit 1 (Screen 1) permitted to assess eligibility, if needed:
   - Hepatitis B virus (HBV), defined by presence of hepatitis B surface antigen (HBsAg);
   - Hepatitis C virus (HCV), defined by presence of hepatitis C antibody (HCVAb), and HCV RNA (when reflexed based on a positive result for HCVAb);

- Human Immunodeficiency Virus (HIV) infection, defined as presence of HIV antibody;
- Known diagnosis of primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome;
- History of esophageal varices, ascites, or hepatic encephalopathy;
- Alcoholic liver disease;
- Wilson's disease, defined as ceruloplasmin level <LLN;
- Known diagnosis of hemochromatosis;
- α-1-antitrypsin (A1AT) deficiency, defined as A1AT level <LLN;
- Prior known drug-induced liver injury;
- Known or suspected hepatocellular carcinoma or other liver cancer;
- History of liver transplant, current placement on a liver transplant list, or current model of end-stage liver disease (MELD) score >12;
- Histological presence of cirrhosis on prior biopsy;

9. Subjects with **any** of the following medical conditions:
   - Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, ileal resection);
   - Diagnosis of type 1 diabetes mellitus;
   - Recent (ie, within the previous 6 months) history of congestive heart failure (New York Heart Association, NYHA, class III or IV) or unstable angina;
   - A history of myocardial infarction, stroke, **or** transient ischemic attack, in the previous 6 months;
   - Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a subject is considered cured if there has been no evidence of cancer recurrence in the previous 5 years;
   - Active placement of medical devices in/on thoracic or abdominal cavities such as pacemakers, defibrillators;
   - Recent history (ie, with the previous 6 months) of ≥2 symptomatic urinary tract infections, as diagnosed by a medical professional, which were pharmacologically managed;
10. Subjects with any anatomical or pathological abnormality that would either preclude or tend to confound the analysis of study data, including any clinically significant abnormal findings on MRI obtained at Visit 2 (Screen 2), by the Sponsor-identified

central imaging vendor, or subjects meeting criteria for contraindication for MRI, including the following:

- History of severe claustrophobia impacting ability to perform MRI during the study despite mild sedation/treatment with an anxiolytic;
- Subjects with metal implants, devices, paramagnetic objects contained within the body, and excessive **or** metal-containing tattoos;
- Subjects unable to lie still within the environment of the MRI scanner or maintain a breath hold for the required period to acquire images despite mild sedation/treatment with an anxiolytic;
- Subjects with abdominal girth greater than the bore size of the site's MRI system.

11. Subjects on any prohibited concomitant medication(s) **or** those unwilling/unable to switch to permitted concomitant medication(s) [refer to Section 5.8];
12. Weight loss of ≥5% within 1 month prior to Visit 1 (Screen 1);
13. Participation in other studies involving investigational drug(s) within 30 days prior to Visit 1 (Screen 1) and up to Visit 9 (on-site Follow-up);
14. Male subjects with partners who are currently pregnant, as well as male subjects who are unwilling or unable to use highly effective method(s) of contraception as outlined in this protocol (Section 4.4.4) for the duration of the study and for **at least 28 days** after the last dose of double-blind IP;
15. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to Visit 1 (Screen 1) **or** during the study until Visit 9 (on-site Follow-up);
16. Subjects with known prior participation in a trial involving PF-06835919 (ie, received at least 1 dose of IP);
17. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study;
18. At Visit 1 (Screen 1), other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or IP administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

At Visit 5 (Day 1), interactive response technology (IRT) will be used to assign each eligible subject a randomization number, with this number recorded on the electronic Case Report Form (e-CRF). A computer-generated randomization code using the method of random permuted blocks will be utilized to randomize subjects 1:1:1 (placebo and 1 of 2 active doses of PF-06835919) prior to the first dose of the double-blind IP provided subjects satisfy **all** of the eligibility criteria outlined in Section 4.1 and Section 4.2.

Subjects must be ≥ 90% compliant (based on pill count) during the 2-week run-in period, as assessed prior to randomization on Day 1 (ie, subjects cannot miss more than 1 dose).

An attempt will be made to equally balance the number of subjects assigned to receive PF-06835919 versus placebo within each stratum by utilizing a 2-tiered stratification scheme. Subjects will be stratified at randomization (Visit 5) based on the presence or absence of T2DM; and by the MRI-PDFF liver fat measurement determined by the Sponsor-identified central imaging vendor of images obtained during Visit 2 (Screen 2):

- Screening liver fat ≥6% and <10%;
- Screening liver fat ≥10%.

4.4. Lifestyle Requirements

After confirmation of eligibility at Visit 2 (Screen 2), and starting at Visit 3 (Run-in), subjects will be instructed to maintain the guidelines described below for the duration of participation in the study. These guidelines must be reiterated at Visit 5 (Day 1).

4.4.1. Diet

- Subjects must abstain from all food and drink (except water) at least 8, but preferably 10 hours, prior to any blood sample collections for clinical laboratory tests;
- Subjects must abstain from all food and drink (except water) for ≥4 hours prior to assessment of liver fat (either via FibroScan® or MRI-PDFF);
- Blinded IP should be administered every day with the morning meal;
- Subjects will be instructed to maintain their normal diet throughout participation in the study (ie, through Visit 9).

4.4.2. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted in moderation as defined in Section 4.2;
- Consumption of caffeinated drinks and nicotine-containing products is permitted during participation in the study; however, there may be a need for brief interruption while at the site and/or Imaging facility, depending on local policy.

4.4.3. Physical Activity

- Subjects will be asked to not engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before blood sample collections for clinical laboratory tests.

- Subjects will be advised to avoid direct sunlight exposure or any high intensity UV light exposure, from the first day of dosing with single-blind IP (Visit 3) and continue until the on-site Follow-up visit (Visit 9). In addition, subjects will be instructed to apply sun cream/lotion with sun protection factor (SPF) of 30 or higher.

4.4.4. Contraception

All fertile male subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness;

2. Correctly placed copper-containing intrauterine device (IUD) or intrauterine system;

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate;

4. Male sterilization with absence of sperm in the postvasectomy ejaculate;

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of IP and continuing for at least 28 days after the last dose of double-blind IP.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and IP identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, IP is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the IP is PF-06835919 and its matching placebo, and will be provided as tablets for oral administration. An IP manual will be provided to the sites prior to the initiation of randomization of subjects into the study.

5.1. Allocation to Treatment

The IRT system will be used to sequentially assign a unique 8-digit subject identification number to each subject who has signed the informed consent document (ICD). This identifying number will be retained throughout the duration of study participation. Allocation of subjects to dosing regimens will proceed through the use of the IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when IP is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files. The study-specific IRT reference manual will be provided prior to first dose and will contain the contact information and further details on the use of the IRT system.

A computer generated randomization schedule will be used to assign approximately 51 subjects to one of the 3 treatment groups described in Table 5 in a randomization ratio of 1:1:1. The randomization number will be recorded in the case report form (CRF). The subject will receive the appropriate study medication assigned by the IRT system.

Table 5. Study Treatment Regimens

Regimen	Dose	25 mg tablets PF-06835919	100 mg tablets PF-06835919	25/100 mg matching placebo tablets
A	Placebo	0	0	3
B	75 mg	3	0	0
C	300 mg	0	3	0

In order to maintain the double-blind design:

- 25 mg, 100 mg, and matching placebo tablets will be the same size and shape;
- Each morning dose will consist of 3 off-white tablets (representing PF-06835919/matching placebo).

5.2. Breaking the Blind

The study will be subject and investigator blinded.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

5.3. Subject Compliance

Compliance of single-blind placebo administration during the Run-in period will be assessed by pill count on Day 1 (Visit 5) for the purpose of inclusion into the study. Acceptable compliance will be defined as self-administration by the subjects of:

- ≥90% of the study-supplied blinded placebo taken by the subject during the Run-In period (ie, Visit 3 to Visit 5)- only 1 dose is permitted to be missed.

Compliance of study medication administration will be assessed during the treatment phase of the study by the number of tablets returned by the subjects at Visit 6, Visit 7, and Visit 8.

- >80% compliance with self-administration of the study medication is expected from Day 1 (Visit 5) to Day 40 (Visit 8); investigators must closely monitor non-compliant subjects in order to enhance their adherence to the study treatment.

Prior to the first dose of single-blind IP, subjects may be provided with a dosing diary and instructed to record the date and time of each daily dose.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

PF-06835919 will be supplied by the Sponsor as 25 mg and 100 mg tablets for oral administration. Matching placebo tablets will also be provided. Investigational product will be supplied in bottles and labeled according to local regulatory requirements.

5.4.2. Preparation and Dispensing

Investigational product is to be dispensed to subjects by qualified site study staff at each clinic visit from Visit 3 to Visit 7, excluding Visit 4. Subjects will receive their first bottle of IP at Visit 3 (single-blind) and will receive a new bottle of IP at each clinic visit through Visit 7, excluding Visit 4 (double-blind). Dosing instructions will be provided to the sites and individual subjects. Upon receipt of the new bottle, the used bottle will be returned. Subjects will be instructed to store the study drug at room temperature and out of the reach of small children.

5.5. Administration

To maintain the blind, administration of IP will use a strategy so that all subjects will receive an equal number of tablets, regardless of which dose they are assigned. Tablets will be active drug (25 mg or 100 mg) or placebo.

Subjects will take a total of 3 tablets of PF-06835919 and/or placebo at approximately the same time each day and recommended to be taken with the morning meal. Subjects will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing. Subject dosing will be witnessed by the investigator site staff at Visit 3, Visit 5, Visit 6, Visit 7, and Visit 8. Subjects will be instructed to delay self-administration of IP on scheduled visit days until they arrive for their outpatient clinic visit. At visits when subjects report to the imaging center, dosing should be delayed until completion of the MRI-PDFF procedure.

Subjects should be instructed that if they forget to take their morning dose at their usual time, they should take the missed dose as soon as possible on the day it was missed, however, there must be at least an 8-hour interval between the missed dose and the next dose. If the subject remembers missing a dose the next day or later, they should be instructed NOT to take 2 doses in the same day.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all IPs are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

IPs should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of IP receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the IP must be quarantined and not used until Pfizer provides permission to use the IP. It will not be considered a protocol deviation if Pfizer approves the use of the IP after the temperature excursion. Use of the IP prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home IPs. The site staff should refer to the IP Manual for additional guidance on storage conditions and actions to be taken when conditions are outside of the specified range.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP supplies. All IP will be accounted for using a drug accountability form/record.

All bottles of blinded IP must be returned to the investigator by the subject at every visit up to Visit 8 (refer to Schedule of Activities).

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused IP (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatments

All concomitant medications taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. Attempts must be made to **not** alter the doses and regimens of chronic background medications after randomization and for the duration of participation in this study. Any changes made to background medications must be captured in the CRF. All subjects must be questioned about concomitant medication at each outpatient visit to the clinical site.

Medications taken before Visit 5 (Day 1) will be documented as prior medications. Medications taken after dosing of double-blind IP at Visit 5 (Day 1) and until the 2nd Follow-up (telephone contact or visit) will be documented as concomitant medications.

5.8.1. Medications for Glycemic Control

Subjects with a diagnosis of T2DM are permitted to be on stable doses of **1 oral agent for glycemic control,** starting at ≥**8 weeks prior to Visit 1 (Screen 1)** and until Visit 9 (on-site Follow-up), including (but not limited to) the following approved classes of agents:

- Biguanide such as metformin;
- Sulfonylureas such as glyburide, acetohexamide, chlorpropamide, tolazamide, tolbutamine, glimepiride, glipizide;
- Dipeptidyl peptidase-4 (DPP-4i) inhibitors such as sitagliptin, saxagliptin, vildagliptin;
- α-glucosidase inhibitors such as acarbose, miglitol.

The use of the following classes of agents is **not** permitted within the timeframes indicated below:

- TZDs such as pioglitazone and rosiglitazone within **8 weeks** prior to Visit 1 and until Visit 9 (on-site Follow-up);

- Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, pramlintide) within **8 weeks** prior to Visit 1 and until Visit 9 (on-site Follow-up);

- Sodium-glucose co-transporter 2 inhibitors such as canagliflozin, dapagliflozin, empagliflozin within **4 weeks** prior to Visit 1 and until Visit 9 (on-site Follow-up)

5.8.2. Lipid-modifying Medications

Subjects are permitted to be on stable doses of the following lipid-modifying agents, starting at ≥ **8-weeks** prior to Visit 1 (Screen 1) and until Visit 9 (on-site Follow-up), including (but not limited to) the following:

- Bile acid sequestrants such as cholestyramine, colestipol, colesevalam;

- Fenofibrate;

- Nicotinic acid / niacin;

The use of the following classes of agents is **not** permitted within the timelines specified:

- Statins such as atorvastatin, simvastatin, rosuvastatin, fluvastatin, pitavastatin, pravastatin within **4 weeks** prior to Visit 1 and until Visit 9 (on-site Follow-up);

- Ezetimibe (OATP substrate) and gemfibrozil (OATP inhibitor) within **4 weeks** prior to Visit 1 and until Visit 9 (on-site Follow-up);

- Monoclonal antibodies inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9), such as alirocumab and evolocumab, within **12 weeks** prior to Visit 1 or within 5 half-lives of dose administered (whichever is longer), and until Visit 9 (on-site Follow-up).

5.8.3. Antihypertensive Medications

Use of background antihypertensive agent(s) is permitted (unless noted below in Section 5.8.5). If possible, doses of antihypertensive agents should be stable for **≥4 weeks** prior to Visit 1 and for the duration of the study, however, starting at Visit 3 (Run-in) some BP medications may be changed, as necessary, to avoid antihypertensive medications not allowed in this study.

5.8.4. Other Acceptable Concomitant Medications

Any subject on the following list of medications must be on stable doses [ie, **≥8 weeks** prior to Visit 1 (Screen 1) and until Visit 9 (on-site Follow-up), if possible]:

- Non-steroidal anti-inflammatory medications (NSAIDs) such as ibuprofen, ketoprofen, diclofenac, naproxen, indomethacin, meloxicam, and celecoxib. Intermittent use of these medications is also permitted;
- Intermittent use of acetaminophen/paracetamol at doses of up to 1 gram per day;
- Inhaled and topical corticosteroids;
- Thyroid replacement therapy and hormone replacement therapy (in eligible female subjects);
- Anti-psychotic medications such as olanzapine, risperidone;
- Antidepressant medications such as tricyclic agents, selective serotonin reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors;
- Vitamin E, including high doses so long as the regimen is stable;
- Certain herbal supplements ***but only*** following consultation with Sponsor;
- Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the Sponsor.

5.8.5. Other Prohibited Concomitant Medications

Subjects must abstain from using the following medications for **≥4 weeks** prior to Visit 1 (Screen 1) and until Visit 9 (on-site Follow-up):

- Use of medications that are known OATP inhibitors including:
    - Rifampin, gemfibrozil, cyclosporine, erythromycin and clarithromycin.
- Chronic use of systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone; and immunosuppressants such as tacrolimus;
- Pharmacological agents with approved indication for weight loss such as orlistat and sibutramine;
- Over-the-counter appetite-simulant or appetite-suppressant, as advertised;
- (Medical-grade) marijuana, regardless of medical indication;
- Specific classes of agents given current study is 1st study in patient population:
    - Coumadin-type anticoagulants *or* other anticoagulants (eg, dabigatran); *though* aspirin at doses ≤325 mg/day is permitted;

- Anticonvulsants;
- Antiarrhythmics, except for beta blockers or calcium channel blockers if used for the management of conditions other than arrythmias;

- Medications historically associated with fatty liver are prohibited if used for **≥4 weeks of continuous use** in the previous 12 months prior to Visit 1 (Screen 1), examples include:
  - amiodarone, methotrexate, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, other known hepatotoxins.

5.9. Rescue Medication

There is no rescue therapy to reverse AEs observed with administration of IP; standard medical supportive care must be provided to manage the AEs.

6. STUDY PROCEDURES

A signed and dated ICD will be obtained from each subject at Visit 1 (Screen 1) before performing any protocol-specific procedures. All requirements and procedures of the trial will be thoroughly reviewed with all subjects. The results of the clinical laboratory assessments and all screening procedures will be evaluated with respect to inclusion and exclusion criteria to determine the subject's eligibility. If a subject does not qualify for the trial, he or she will be considered a screen failure. **Adverse Event (AE) reporting, including Serious Adverse Event (SAE) reporting will begin from the time the ICD is signed at Visit 1 (Screen 1).**

For the procedures described below, where multiple procedures are scheduled at the same time points relative to dosing, the following chronology of events should be adhered to as much as possible:

- ***12-lead ECG:*** obtain prior to vital signs assessment, blood samples, and prior to dosing [refer to Section 7.4];
- ***Vital Signs (BP, pulse rate)*:** obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing [refer to Section 7.5];
- ***Fasting blood samples, including PK*:** after assessment of 12-lead ECG and vital signs but prior to dosing;
- ***Other pre-dose procedures*:** should be obtained/performed as close as possible to the scheduled time, but may be obtained before or after blood specimen collection;
- ***Dosing of blinded IP*:** must occur after any pre-dose blood sample collections.

6.1. Screening (Visits 1 and 2)

For Visit 1, subjects will be instructed to arrive at the study site after at least an 8-hour, but preferably 10-hour fast (except water).

After obtaining informed consent for all subjects at Screen 1, liver fat will be estimated by FibroScan®. If a subject's CAP™ measurement is <260 dB/m, the subject will be deemed ineligible and not undergo any additional screening assessments. If the subject has a CAP™ value ≥260 dB/m, all study procedures outlined in the Schedule of Activities should be completed for Visit 1.

Screen 2 (Visit 2) will occur only after subjects are identified to be eligible for the study following assessments conducted at Screen 1. Subjects will be instructed to report to the Imaging facility after a minimum 4-hour fast to undergo liver fat assessment via MRI-PDFF.

In rare cases, subjects may be re-screened, however this is permitted only when, due to logistical constraints, the maximum period between Visit 1 to Visit 5 (ie, Screen 1 to Day 1) exceeds 8 weeks. In such cases, all screening procedures must be repeated and the subject assigned a new 8-digit study-specific subject identification number (SSID) number. Subjects must be deemed to meet all the eligibility criteria including assessment of liver fat via MRI-PDFF at Screen 2 visit, under the new 8-digit SSID number.

6.2. Run-in Period (Visit 3)

After the investigator has determined eligibility criteria have been satisfied (approximately 1 week following Visit 2), subjects will return to the site after a minimum 8-hour, but preferably 10-hour fast (except water). The Run-in period will serve to familiarize the subject with the study treatment regimen and exclude subjects who are not compliant with dosing. This visit will occur 14±2 days prior to the planned date of randomization (Visit 5, Day 1).

For all subjects, refer to the Schedule of Activities for the study procedures to be completed at the Run-in visit (Visit 3).

Following completion of the above procedures, single-blind IP will be self-administered while witnessed by adequately trained site staff. Subjects will then be discharged from the site with enough IP to last until Day 1 (Visit 5).

During the approximate 14-day Run-in period (timing dependent on site and subject logistics), subjects will complete a 24-hour urine collection to measure fructose excretion (refer to Section 7.8.10). Subjects will report to the study site and be instructed to fully empty their bladders, and then be provided with containers and instructions to collect ALL of their urine during the subsequent 24 hours. Subjects will return to the study site approximately 24 hours later to empty their bladders and complete the urine collection.

6.3. Baseline MRI-PDFF (Visit 4)

Between 2 to 6 days, inclusive, prior to Visit 5 (Day 1), subjects will be instructed to report to the Imaging facility following a ≥4-hour fast, and within ±2 hours of the Visit 2 time to

undergo liver fat assessment via MRI-PDFF. Subjects should self-administer single-blind IP post- MRI-PDFF.

6.4. Study Period

6.4.1. Day 1 (Visit 5)

Approximately 14 days from Visit 3, subjects will return to the site after a minimum of an 8-hour, but preferably 10-hour fast and within ±2 hours of the Visit 1 time. Subjects will be asked to return IP dispensed at Visit 3 for an assessment of the pill count. Subjects must be at least 90% compliant with the placebo run-in IP in order to be randomized.

Refer to the Schedule of Activities for the study procedures to be completed prior to administration of IP on Day 1. Be sure to collect a genomic banked biospecimen. If missed, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

Subjects who meet all entry criteria will be randomized to double-blind study treatment on Day 1. Sites will contact the IRT system for assignment of double-blind treatment. Following witnessed dosing of IP, an approximate 2-week supply of double-blind IP will be dispensed, and subjects will be discharged from the site.

6.4.2. Day 14 (Visit 6)

At 14±2 days from Visit 5, subjects will return to the study site after a minimum of an 8-hour, but preferably 10-hour fast and within ±2 hours of the Visit 5 time.

Refer to the Schedule of Activities for the study procedures to be completed prior to administration of IP on Day 14.

Following completion of the above procedures, double-blind IP will be dispensed to subjects via IRT and self-administered. Subjects will then be discharged from the study site with an approximate 2-week supply of double-blind IP.

6.4.3. Day 28 (Visit 7)

At 28±2 days from Visit 5, subjects will return to the study site after a minimum of an 8-hour, but preferably 10-hour fast and within ±2 hours of the Visit 5 time. Within 24 hours of this visit, subjects will complete a 24-hour urine collection to measure fructose excretion (refer to Section 7.8.10). Subjects will be instructed to fully empty their bladders, and will then be provided with containers and instructions to collect ALL of their urine during the subsequent 24 hours. Subjects will return to the study site approximately 24 hours later to empty their bladders, complete the urine collection, and have a blood sample collected for PK analysis prior to dosing. It should be noted that 2 PK samples will be collected around this visit; one at approximately the start of the urine collection; and a second one at approximately the end of the urine collection (24 hours later). If necessary for logistics, it is acceptable for subjects to report to the study site 24 hours prior to the nominal Day 28 visit to begin the urine collection, and then complete it at the Day 28 visit.

Refer to the Schedule of Activities for the study procedures to be completed prior to administration of IP on Day 28.

Following completion of the above procedures, double-blind IP will be dispensed to subjects via IRT and self-administered. Subjects will then be discharged from the study site with an approximate 2-week supply of double-blind IP.

6.4.4. Day 40 (Visit 8)

Within approximately 24 hours prior to the Day 40 visit, or on the day of the Day 40 visit, subjects will be instructed to report to the Imaging facility following a ≥4-hour fast, and within ±2 hours of the Visit 4 time to undergo liver fat assessment via MRI-PDFF. Subjects should self-administer double-blind IP post- MRI-PDFF.

At 40±2 days from Visit 5, subjects will return to the study site after a minimum of an 8-hour, but preferably 10-hour fast and within ±2 hours of the Visit 5 time.

Refer to the Schedule of Activities for the study procedures to be completed prior to administration of IP on Day 40.

Following completion of the above procedures, subjects will receive their final dose of double-blind IP from the supply dispensed at the previous visit. Subjects will then be discharged from the study site.

6.5. Follow-up Visit (Visit 9)

At ≥7 days and ≤14 days following the last dose of double-blind IP, subjects will return to the study site for a follow-up visit after a minimum 8-hour, but preferably 10-hour fast and within ±2 hours of the Visit 5.

Refer to the Schedule of Activities for the study procedures to be completed at this visit.

6.5.1. Follow-up Contact

A Follow-up contact via telephone of all subjects will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of double-blind IP.

Refer to the Schedule of Activities for the study procedures to be completed during this contact.

- ***NOTE*:** this contact can be considered as on-site in order to permit follow-up of open AEs and/or abnormal laboratory tests from prior visit(s), as needed.

6.6. Subject Withdrawal

In this study, any subject who discontinues participation in the trial anytime prior to administration of double-blind IP will have no additional procedures completed. However, an early termination visit is to be considered for all subjects who were randomized *and* received at least 1 dose of the double-blind IP, *and then* are prematurely withdrawn from the

study. Subjects should return to the site for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw but ≤14 days after last dose of double-blind IP. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the assessments outlined in the Schedule of Activities. Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of IP or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also Section 8.1.3) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts

must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused IP, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed at times outlined in the Schedule of Activities. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 6. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
− Hemoglobin − Hematocrit − RBC count − MCV − MCH − MCHC − Platelet count − WBC count − Total neutrophils (Abs) − Eosinophils (Abs) − Monocytes (Abs) − Basophils (Abs) − Lymphocytes (Abs)	− BUN − Creatinine − *Plasma* glucose (fasting) − Calcium − Sodium − Potassium − Chloride − Total CO_2 (Bicarbonate) − AST − ALT − GGT − Alkaline phosphatase − Total Bilirubin − Direct (conjugated) bilirubin[a] − Indirect (unconjugated) bilirubin[a] − Uric acid − Albumin − Total protein	− pH − Glucose (qual) − Protein (qual) − Blood (qual) − Ketones − Nitrites − Leukocyte esterase − Urobilinogen − Urine bilirubin − Microscopy	At Screen 1 only: − Coagulation: (PT, INR, aPTT) − Serum FSH (females) − Urine drug test[b] − Serology: HBsAg, HCV Ab (and if positive, reflex HCV RNA), HIV − A1AT − Ceruloplasmin
Additional Tests (Needed for instances of suspected Hy's law)			
	− AST, ALT (repeat) − Total bilirubin (repeat) − Albumin (repeat) − Alkaline phosphatase (repeat) − Direct bilirubin − Indirect bilirubin − Creatine kinase − GGT − PT/INR − Total bile acids − Acetaminophen drug levels − And/or protein adduct level		

a. Direct and indirect bilirubin measured only when total bilirubin is >ULN
b. Minimum requirement for urine drug test include cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines

For list of abbreviations, refer to Appendix 1

Additional laboratory results may be reported on these samples as a result of the method of analysis **or** the type of analyzer used by the Sponsor-identified central laboratory or secondary laboratory; **or** as derived from calculated values. These additional tests would *not* require additional collection of blood.

Unscheduled clinical laboratory tests for subject safety may be obtained at any time during the study to assess any perceived safety concerns and shipped to the Sponsor-identified central laboratory for analysis.

Additional details regarding sample collection, processing, and shipment will be provided in the study-specific central laboratory manual to be provided prior to the start of the study.

7.2. Physical Examination

In this study, physical examinations are to be performed at nominal time points specified in the Schedule of Activities. Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. Height will also be measured as part of the physical examination at Screen1 (Visit 1). A limited physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

7.2.1. Measurement of Waist Circumference

As part of the physical examination at Screen 1 only, waist circumference will be measured using a flexible anthropometric tape and ideally, reporting the measurement in centimeters with accuracy to the nearest 0.1 centimeter. Measurement will be undertaken as follows:

- While subject is in a standing position with arms resting comfortably at the side;
- Under standard conditions including post-void, with the tape touching the skin (not clothing);
- At the end of a normal expiration (when lungs are at their residual capacity).

The measurement will consider the following anatomical features as benchmarks:

- Circumference of the narrowest part of the torso as viewed from the anterior aspect **or;**
- If the narrowest part of the torso cannot be identified, the measurement must be made of the smallest horizontal circumference in the area between the ribs and the iliac crest.

7.3. Body Weight

In this study, assessment of body weight will occur at the nominal time points specified in the Schedule of Activities per the following specifications:

- Weight will be recorded using a scale placed on a stable, flat surface;
- Same scale, as much as practically possible, will be used with the scale reporting weight in kilograms or pounds, and accuracy to the nearest 0.1 kg (or 0.2 pounds), ie, the device used for this study must be able to distinguish a difference between 68.4 kg and 68.3 kg;
- Measurement must be undertaken:
  - At approximately the same time of the day at each nominal time point;
  - After the subject has been asked to void (ie, forced void);

- Under standard conditions (eg, subjects must wear light clothing with content of their pockets emptied or hospital gown **and not** be wearing shoes or bulky layers of clothing/jackets);

7.4. 12-lead Electrocardiogram

In this study, 12-lead ECGs will be collected at the nominal time points specified in the Schedule of Activities per the following specifications:

- All scheduled 12-lead ECGs should be performed after the subject has rested quietly for ≥10 minutes in a supine position;

- Further ECG monitoring will occur if a) a post-dose QTc interval is increased by ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remains above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

In some cases, it may be appropriate to repeat abnormal 12-lead ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

7.5. Blood Pressure and Pulse Rate

In this study, assessment of vital signs (including seated BP, and pulse rate) will occur at the nominal time points specified in the Schedule of Activities per the following specifications:

- At the Screen 1 visit only, the subject's arm circumference should be measured at the midpoint of the length of the upper arm using a flexible anthropometric tape to select the appropriate cuff to be used throughout the study to measure BP/pulse rate via an automated device using an oscillometric method (not auscultation);

  - Subjects with arm circumference greater than the largest cuff size available at each study site are not eligible.

- Seated BP/pulse rate will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg, following a rest of **≥5 minutes**;

- Same arm (preferably the dominant arm) will be used for BP/pulse rate assessment throughout the study;

- Subjects should be instructed not to speak during BP/pulse rate measurements.

Additional collection times, or changes to collection times of BP/pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

7.6. Liver Fat Assessments

7.6.1. Assessment of Liver Fat and Stiffness Using FibroScan®

In this study, estimation of liver fat and stiffness using FibroScan® will occur at scheduled visits outlined in the Schedule of Activities. Each acquisition will take approximately 10 minutes and require the subjects to be in a supine position with the right arm placed flat above the head. Acquisition results do *not* need independent over-read, but steps to ensure the acquisition was complete and accurate are required, as per training to be provided by EchoSens (vendor supporting the device) at the start of the study. As much as practically possible, attempts will be made to ensure each individual subjects' assessment is performed by the same site staff.

Complete details regarding acquisitions using FibroScan® to assess CAP™ and LSM will be provided by EchoSens before initiation of this study. All images acquired must be saved by the study site until the conclusion of the study; the summary of numerical results (including quality-related outputs) must be printed and saved by the study site (or Imaging facility, as applicable) as part of each subject's source documents.

7.6.2. Assessment of Liver Fat Using MRI-PDFF Acquisition and Analysis

At scheduled visits (refer to the Schedule of Activities), liver fat and stiffness will be assessed via MRI, using the PDFF acquisition protocol.

Across the study sites selected for this study, the Sponsor-identified central imaging vendor will train the staff at the Imaging facility on the MRI-PDFF acquisition protocol, on just-in-time review of the acquired images for assessment of images being deemed evaluable, and on transfer (preferably electronically) of the images to the Sponsor-identified central imaging vendor for analysis and quantification of liver fat. **Only the staff members at the Imaging facility who are trained by the Sponsor-identified central imaging vendor are permitted to acquire images in the subjects who consent for this study,** however in rare/limited situations, exceptions may be granted with written approval of the Sponsor. Complete details on the MRI-PDFF acquisition protocol, determination of quality of images, and transmission of data to Sponsor-identified central imaging vendor will be provided in an Imaging Manual offered to the study sites prior to the start of the study.

As much as practically possible, analysis of the MRI-PDFF images acquired from baseline (Visit 4) to Visit 8 (Week 6) will be undertaken by a single colleague at the Sponsor-identified central imaging vendor who will be blinded to individual subject's clinical data, as well as randomization and stratification assignment.

7.6.3. Analysis of MRI-PDFF Images Including Determination of Eligibility

A subject's eligibility for this study based on liver fat as assessed via MRI-PDFF at Screen 2 will be made by the Sponsor-identified central imaging vendor, only. The individual subject's liver fat will not be communicated to the study site, only the stratum to which the

subject is assigned (though results from Screen 2 will be known to the Sponsor). In the case of the MRI at Screen 2, study sites will only be informed whether a subject meets eligibility criteria or if the screening MRI should be repeated once, as determined by the Sponsor-identified central imaging vendor. For all subsequently scheduled MRI-PDFF assessments, study sites will only be informed whether the images are deemed evaluable (or not). Of note, subjects with non-evaluable baseline images (as determined by the Sponsor-identified central imaging vendor) may be withdrawn prior to or after randomization, at the discretion of the Sponsor.

7.6.4. Management of Incidental Findings

An incidental finding is one unknown to the subject that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study.

The MRIs will be reviewed by the Sponsor-identified central imaging vendor. The purpose of this review is to evaluate images for the amount of fat in the liver. Central image review is not a complete medical review of the subject. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study Sponsor for disclosure to the principal investigator. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the study site or those with an existing physician-patient relationship. The principal investigator will be responsible for reporting any AEs identified from incidental findings as described in the Adverse Event Reporting section. Identification of such incidental findings during the central review process should not be expected, and the study site maintains responsibility for performing a general safety review of all images as per study site protocols.

7.6.5. Post-hoc Analyses

As a means to understand the performance of CAP™ via FibroScan®, MRI-PDFF, and each of these liver assessment techniques relative to the other, the Sponsor and/or delegate may undertake post-hoc analyses of the subject-level, coded data acquired in this study. Any such analyses will not be included in the clinical study report; but a separate supplemental report will be written to capture this work, if undertaken.

CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the IP under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the IP under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the IP(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an IP under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a

subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving IP), through and including a minimum of 28 calendar days after the last administration of the IP.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to IP must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the IP caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the IP caused the event, then the event will be handled as "related to IP" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to IP, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

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

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg,

from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

- Hospitalization does not include the following:
- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE

requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

- In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

- The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the IP During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the IP under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the IP; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the IP;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the IP prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the IP, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer

Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

- If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

- Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the IP.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the IP under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the IP by the wrong subject, or at the wrong time, or at the wrong dosage strength.

- Medication errors include:
- Medication errors involving subject exposure to the IP;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the Sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Approximately 17 subjects per arm are planned to be enrolled in this study for a total of approximately 51 subjects. This assumes an approximate 15% dropout rate resulting in 14 completers per arm. With this sample size the power to detect a 25% mean reduction in MRI-PDFF compared to placebo is at least 90% using a 2-sample t-test and a 2-sided Type I error rate of 0.1. This calculation assumes the pooled standard deviation (SD) to vary from 12% (based on study NCT01431521) to 22% (based on an internal study). The power will be at least 80% if the SD is in the range of 23% - 25%.

9.2. Efficacy Analysis

The primary analysis population for all efficacy analyses will include all randomized subjects who received at least 1 dose of study medication (Full Analysis set).

9.2.1. Analysis of the Primary Endpoint

The primary endpoint will be the percent change from baseline at Week 6 in MRI-PDFF. Baseline will be the closest measurement prior to first dose on Day 1. An analysis of covariance (ANCOVA) will be performed with treatment as a factor, baseline MRI-PDFF value and baseline diabetes status as covariates. Baseline fructose excretion and its interaction with treatment will be considered to be included as the additional covariates. Estimates of the mean differences between each active dose and placebo at Week 6, and the corresponding 90% CI will be obtained from the model. Both comparisons of PF-06835919 doses with the placebo will be performed at a Type I error rate of 10% (2-sided). No adjustment for multiple comparisons will be made.

Descriptive summaries of the observed values, change and percent change from baseline in MRI-PDFF in each treatment group will also be produced.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

9.4. Safety Analysis

All subjects who receive at least 1 dose of double-blind IP will be included in the safety analyses and listings.

Adverse events (including SAEs), ECGs, BP, pulse rate, and clinical laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Safety data will be presented in tabular and/or graphical format and summarized descriptively, according to Sponsor's reporting standards.

Physical examination information collected during the course of the study will not be captured for inclusion into the study database via the CRF/DCT (data collection tool) page. However, any untoward findings identified on physical examinations conducted after the administration of the first dose of IP will be captured as an AE, if those findings meet the definition of an AE.

9.4.1. Electrocardiogram Analysis

The heart rate, PR, QRS, QT,and QTc intervals will be recorded at each assessment time indicated in the Schedule of Activities. QTcF will be derived using Fridericia's heart rate correction formula.

The maximum value (post dose) and the maximum increase from baseline for QTcF, PR and QRS will be determined from overall measurements taken post dose. These data will be summarized descriptively by treatment using categories as defined in the statistical analysis plan. Numbers and percentages of subjects meeting the categorical criteria will be provided and individual values listed in the study report.

No formal inferential statistics will be applied to the ECG data.

9.4.2. Vital Signs

Seated BP and pulse rate will be recorded at each assessment time indicated in the Schedule of Activites.

Baseline will be the pre-dose measurement prior to first dose on Day 1. Maximum values and maximum changes from time-matched baseline for vital signs will be summarized descriptively by treatment using categories as defined in the statistical analysis plan. Numbers and percentages of subjects meeting categorical criteria outlined in the SAP will be

provided and individual values listed in the study report. No formal inferential statistics will be applied to the vital signs data. Descriptive summaries of the observed values and change from baseline at each time point in each treatment group will also be produced.

9.5. Interim Analysis

No interim analysis will be conducted in this study.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to

third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the IP, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV) – the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subjects to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or IP safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06835919 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: {229800}: {June 2016}: World Wide Web URL: http://omim.org/.

2. Sachs B, Sternfeld L, Kraus G. Essential fructosuria: Its pathophysiology. Am J Dis Child 1942;63:252-69.

3. Boesiger P, Buchli R, Meier D, et al. Changes of liver metabolite concentrations in adults with disorders of fructose metabolism after intravenous fructose by ^{31}P magnetic resonance spectroscopy. Pediatr Res 1994;4:436-40.

4. Abdelmalek MF, Lazo M, Horska A, et al. Fatty Liver Subgroup of Look, A. R. G., Higher dietary fructose is associated with impaired hepatic adenosine triphosphate homeostasis in obese individuals with type 2 diabetes. Hepatology 2012;56:952-60.

5. Maenpaa PH, Raivio KO, Kekomaki MP. Liver adenine nucleotides: fructose-induced depletion and its effect on protein synthesis. Science 1968;161:1253-4.

6. Lanaspa MA, Sanchez-Lozada LG, Choi YJ, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. J Biol Chem 2012;287:40732-44.

7. Erion DM, Popov V, Hsiao JJ, et al. The role of the carbohydrate response element-binding protein in male fructose-fed rats. Endocrinology 2013;154:36-44.

8. Softic S, Cohen DE, Kahn CR. Role of dietary fructose and hepatic de novo lipogenesis in fatty liver disease. Dig Dis Sci 2016;61:1282-93.

9. Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 2009;119:1322-34.

10. Abid A, Taha O, Nseir W, et al. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. J Hepatol 2009;51:918-24.

11. Assy N, Nasser G, Kamayse I, et al. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. Can J Gastroenterol 2008;22:811-6.

12. Schwarz JM, Noworolski SM, Wen MJ, et al. Effect of a high-fructose weight-maintaining diet on lipogenesis and liver fat. J Clin Endocrinol Metab 2015;100:2434-42.

13. Lustig R, Mulligan K, Noworolski SM, et al. Isocaloric fructose restriction and metabolic improvement in children with obesity and metabolic syndrome. Obesity 2016;24:453-60.

14. Stanhope KL, Medici V, Bremer AA, et al. A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults. Am J Clin Nutr 2015;101:1144-54.

15. Sanyal AJ, Friedman SL, McCullough AJ, et al. American Association for the Study of Liver Diseases, United States Food and Drug Administration. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations from an American Association for the Study of Liver Diseases-U.S. Food and Drug Administration Joint Workshop. Hepatology 2015; 61:1392-05.

16. Ishimoto T, Lanaspa MA, Le MT, et al. Opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. Proc Natl Acad Sci USA 2012;109:4320-5.

17. Ishimoto T, Lanaspa MA, Rivard CJ, et al. High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. Hepatology 2013;58:1632-43.

18. Duan P, Zhao P, Zhang L. Physiologically based pharmacokinetic (PBPK) modeling of pitavastatin and atorvastatin to predict drug-drug interactions (DDIs). Eur J Drug Metab Pharmacokinet 2016;Nov:1-17.

19. Noureddin M, Lam J, Peterson MR et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology 2013;58:1930-40.

20. Le TA, Chen J, Chanqchien C, et al. Effect of colesevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. Hepatology 2012; 56:922-32.

21. Loomba R, Sirlin CB, Ang B, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART Trial). Hepatology 2015;61:1239-50.

22. Stanhope KL, Schwarz JM, Keim NL et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 2009;119 (5):1322-34.

23. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55(6):2005-23.

24. Petit JM, Cercueil JP, Loffroy R, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes. The Lira-NAFLD study. J Clin Endocrinol Metab 2017; doi:10.1210/jc.2016-2775.

Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
A1AT	α-1-antitrypsin
Abs	absolute
ADP	adenosine diphosphate
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ANCOVA	analysis of covariance
ApoB	apolipoprotein B
ApoC3	apolipoprotein C3
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{24}	systemic exposure over 24 hours
AUEC24	area under the effect curve over 24 hours
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CAP	controlled attenuation parameter
ChREBP	carbohydrate-responsive element-binding protein
CI	confidence interval
CK	creatine kinase
CLp	plasma clearance
C_{max}	maximum concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
dB/m	decibels per meter
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury

Abbreviation	Term
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DPP-4i	dipeptidyl peptidase-4 inhibitors
DU	dispensable unit
EC_{50}	50% of the maximum effect
EC	ethics committee
ECG	electrocardiogram
e-CRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EFD	embryo-fetal development
E_{max}	efficacy
EU	European Union
EudraCT	European Clinical Trials Database
F1P	fructose-1-phosphate
F	bioavailability
FIH	first in human
FSH	follicle-stimulating hormone
f_u	unbound plasma fraction
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GLP-1r	glucagon-like peptide 1 receptor
HbA1c	hemoglobin A1C
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatic cellular carcinoma
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HDL-C	high-density lipoprotein cholesterol
HEK	human embryonic kidney
HepB	hepatitis B
HepC	hepatitis C
hERG	human Ether-a-go-go related gene
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
hs-CRP	high-sensitivity C-reactive protein
IC_{50}	50% of the inhibition concentration
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IDL	intermediate-density lipoprotein

Abbreviation	Term
IL-6	interleukin 6
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IWR	interactive web response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
KHK	ketohexokinase
Ki	inhibitory constant
kPa	kilopascals
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
LFT	liver function test
LSLV	last subject last visit
LSM	liver stiffness measure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MELD	model of end-stage liver disease
MMRM	mixed model repeated measures
MOA	mechanism of action
MRI	magnetic resonance imaging
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
ND	not determined
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSAID	non-steroidal anti-inflammatory
NYHA	New York Heart Association
OAT	organic anion-transporter
OATP	organic anion-transporting polypeptide
OMIM	Online Mendelian Inheritance in Man
PCD	primary completion date
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PDE	phosphodiesterase

Abbreviation	Term
PDFF	proton density fat fraction
P-gp	P-glycoprotein
PGx	pharmacogenomic(s)
PI	principal investigator
PK	pharmacokinetic
PT	prothrombin time
QD	once daily
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	standard operating procedure
SPF	sun protection factor
SRSD	single reference safety document
SSID	study-specific subject identification number
SUSAR	suspected unexpected serious adverse reaction
t½	terminal half-life
T2DM	Type 2 Diabetes Mellitus
TBili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to reach maximum concentration
TRLP	triglyceride-rich lipoprotein particles
TZD	thiazolidinediones
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
US	United States
UV	ultraviolet
VLDL	very low-density lipoprotein
VCTE	vibration controlled transient elastography
V_{ss}	volume of distribution
WBC	white blood cells