A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 3-ARM, PARALLEL GROUP STUDY TO EVALUATE SAFETY, TOLERABILITY AND PHARMACODYNAMICS OF PF-06835919 ADMINISTERED DAILY FOR 16 WEEKS IN ADULTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND TYPE 2 DIABETES MELLITUS ON METFORMIN

Investigational Product Number:	PF-06835919
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	C1061011
Phase:	2a

Short Title: Phase 2a, 3-arm, 16-week, double-blind safety and pharmacodynamic study in adults with non-alcoholic fatty liver disease and type 2 diabetes mellitus

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	21 March 2019	N/A
Amendment 1	23 July 2019	Section 1.3. (Schedule of Activities [SoA]) will now state that the Day 112 visit window will only permit 3 days prior to, but not following visit (Site window -3), to prevent subjects to be off of study drug for 3 days before end-of-study procedures are conducted. A protocol administrative change letter (PACL) was previously written to describe this change. Section 2.3. (Benefit/Risk Assessment) will be changed to reflect the protocol's design and inclusion/exclusion criteria to exclude women of child bearing potential (WOCBP) from this study. Previous wording was erroneously included from an earlier study, and inconsistent with the remainder of the protocol. The previously issued PACL described this change.  Section 5.1. (Inclusion Criteria) will be changed to use centimeters instead of inches to describe the waist circumference requirements for male and female participants, consistent with the units describe elsewhere in the protocol. Section 5.2. (Exclusion criteria) for LDL-C has corrected the SI value unit conversion (now reading 4.92 mmol/L). Section 9.4.1 (Efficacy Analysis) of secondary

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		endpoints now includes modeling details: The derived endpoints will be analyzed using MMRM with treatment, time and treatment by time interaction as fixed effects and baseline value as a covariate. Additional covariates, if considered for inclusion in the model, will be described in the SAP. Section 10.2. Appendix 2 (Clinical Laboratory Tests) will remove ALT and glucose as blinded parameters, as there is no significant risk of unintentional blinding based on these parameters. The previously issued PACL described this change. Section 10.4.1. Appendix 4 (Male Participant Reproductive Inclusion Criteria) will be changed to state that, in addition to male condom use, a highly effective method of contraception is *required* (previously 'considered') for WOCBP partners of male participants. Section 10.4.4. Appendix 4 (Contraception Methods) has been changed to remove reference to user dependency, and to no longer permit the following methods of contraception in potentially child-bearing female partners of male participants: Progestogen only oral hormonal contraception where inhibition of ovulation is not the primary mode of action; Male or female condom with or without spermicide; Cervical cap, diaphragm, or sponge with spermicide; A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods). These methods by themselves would not be considered highly effective.

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 2	11 September 2019	Incorporation of results of C1061016 midazolam drug-drug interaction study to relevant background sections, and based on the results of this study, removal of relevant restrictions of CYP3A4 concomitant medications, given that clinical results indicate PF-06835919 does not induce 3A4 metabolism. Specific changes are as follows: 2.2.1. (Nonclinical Overview) has now been revised to no longer indicate the potential for CYP3A4 induction with PF-06835919. 2.2.2. (Clinical Overview) now makes reference to the C1061016 study, alongside other completed clinical studies. 2.2.3. (Preliminary Pharmacokinetic Results of PF-06835919-Midazolam Drug-Drug Interaction Study [C1061016]) has been added as a new subheading within the Clinical Overview, to provide a summary of the results of this study, including a stable on the effect of PF-06835919 on midazolam pharmacokinetic parameters. 4.3. (Justification for Dose) now states that there is not expected to be any effect of PF-06835919 on the PK of CYP3A4 substrates, and has removed reference to the former concomitant medication restrictions, accordingly. 6.5. (Concomitant Therapy) has been updated to; remove the previous caution of potential altered exposure of lipid-modifying agents that are 3A4 substrates; lift the restrictions on antihypertensive agents that are significantly metabolized by 3A4; remove text in section on Other Prohibited Concomitant Medications which previously stated potential altered exposure of sensitive 3A4 substrates.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

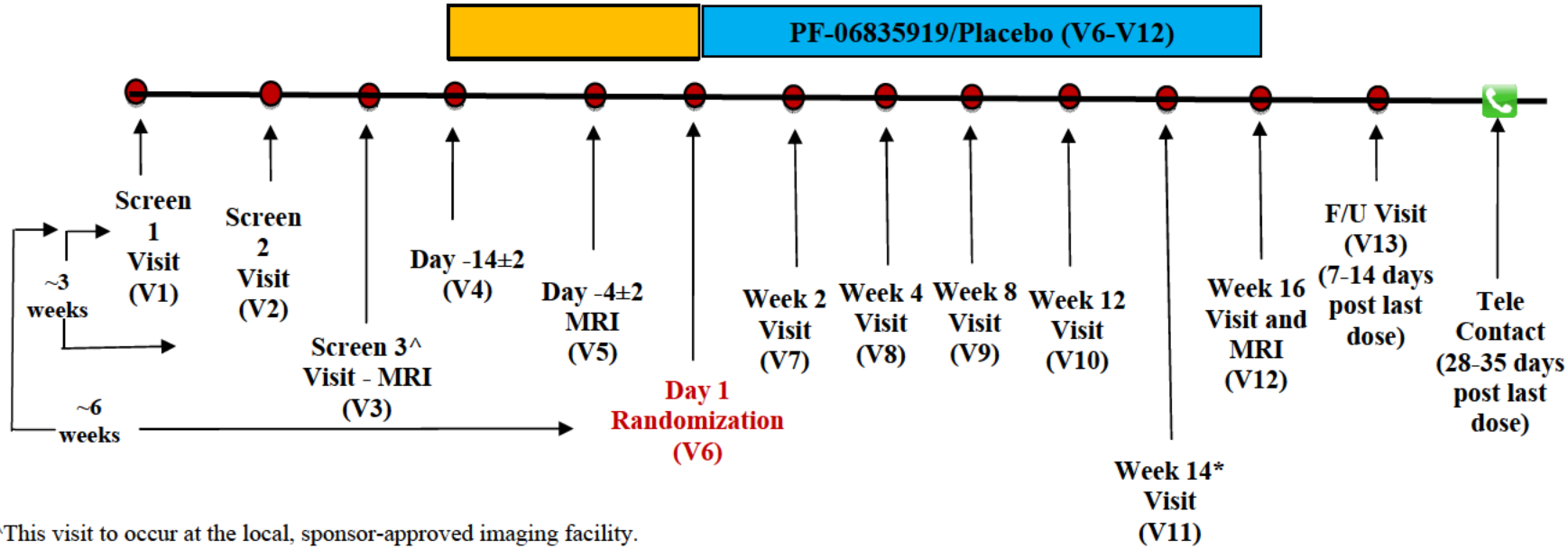
1.1. Synopsis

Since all sites conducting the study will be located in North America, this is considered not applicable (N/A).

1.2. Schema

The overall study design is captured below in Figure 1.

Figure 1. Study C1061011 Design



^This visit to occur at the local, sponsor-approved imaging facility.

*This visit is only applicable to participants involved in the sub-study. Participants will return to the site for distribution of food and water diary, placement of devices, receive instructions for use, and report AEs. IP does not need to be administered at the site.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to Section 8 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 in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier	Screen 1	Screen 2	Screen 3	Run-In	Baseline	Treatment Phase[a]							Follow-up		Early Termination
Week Relative to Dosing on Day 1				-2	-1	0	2	4	8	12	14[c]	16	17-18	20-21[b]	
Day Relative to Dosing on Day 1				-14±2	-4±2	1	14±2	28±3	56±3	84±3	98±3	112-3	--	--	
Visit to Site	1	2	3	4	5	6	7	8	9	10	11	12	13	--	
Informed consent & demography	x														
Assign SSID (via IRT)	x														
Medical & medication history (update)	x			x		x	x	x	x	x		x	x	x	x
Liver fat and stiffness (via FibroScan®)	x	x				x						x			x[d]
Liver fat (via MRI-PDFF)			x		x							x[e]			x[d]
Physical examination[f]	x			x								x	x		x
Confirm contraceptive method	x			x		x	x	x	x	x		x	x	x	x
Serious & non-serious AE monitoring	x	→	→	x	→	x	x	x	x	x	x	x	x	x	x
Body weight	x			x		x	x	x	x	x		x	x		x
Single, supine 12-lead ECG (after ≥10 minutes rest)	x			x		x		x	x	x		x	x		x
Triplicate, seated vitals (BP & pulse rate; after ≥5 minutes rest)	x			x		x	x[g]	x	x[g]	x[g]		x	x		x
Sub-study device distribution/placement and monitoring[h]				x	→	x					x	x			
Sub-study food and water diary distribution/maintenance				x	→	x					x	x			
Randomization in trial (via IRT)						x									
Dispense IP (via IRT)				x		x	x	x	x	x					
Witnessed dosing on site of IP, including meal				x		x	x	x	x	x		x			
Administration of IP				x	→	x	→	→	→	→	→	x			
Dosing diary distribution (Visit 4), maintenance, and review				x	→	x	→	→	→	→	→	x			
Train on use and dispense (unless participant-provided) glucometer & ancillary supplies				x											
Counseling on diet/exercise guidelines				x		x									

Visit Identifier	Screen 1	Screen 2	Screen 3	Run-In	Baseline	Treatment Phase[a]							Follow-up		Early Termination
Week Relative to Dosing on Day 1				-2	-1	0	2	4	8	12	14[c]	16	17-18	20-21[b]	
Day Relative to Dosing on Day 1				-14±2	-4±2	1	14±2	28±3	56±3	84±3	98±3	112-3	--	--	
Visit to Site	1	2	3	4	5	6	7	8	9	10	11	12	13	--	
Compliance via pill count of returned IP						x	x	x	x	x		x			x
Blood Collections after ≥8-hour fast															
Clinical laboratory tests	x			x		x	x	x	x	x		x	x		x
FSH (females), HBsAg, HCV Ab (and if positive, reflex HCV RNA), HIV, coagulation, α1-antitrypsin, ceruloplasmin	x														
Lipid panel,[1] HbA1c, insulin, hs-CRP	x			x		x	x	x	x	x		x	x		x
Thyroid panel (TSH and free T4)						x						x			x
CCI [redacted]						[redacted]									
Urine Collections															
Urine drug test	x														
Urine for albumin-to-creatinine ratio						x			x			x	x		x
Urinalysis, including microscopy	x			x		x	x	x	x	x		x	x		x

a. All procedures before morning dose of IP and metformin.
b. Telephone call unless PI deems a visit is necessary. Must occur 28-35 days from administration of the final dose of double-blind IP.
c. Visit required only for participants in the substudy.
d. Procedures to be performed if participants have completed at least 8 weeks of double-blind administration (Visit 9).
e. MRI-PDFF assessment to be performed within approximately 48 hours prior to Visit 12, or on the same day as Visit 12.
f. Includes arm and waist circumference, and height at Visit 1 only. Complete physical examination at Screen 1 (Visit 1), Week 16 (Visit 12), and early termination, or at other visits if deemed necessary by the PI. Limited physical examinations at all other visits when required per SoA.
CCI [redacted]
h. Select participants across select sites in the US will have 2 wearable sensors allocated: a continuous glucose monitor, and a wrist-worn, watch-type device to measure activity and heart rate, both to be worn continuously for up to 14 days (duration depending on the device used; details and instructions will be provided in a manual prior to study start), during the run-in period and between Weeks 14 and 16.
i. Lipid panel includes total cholesterol, direct LDL-C, HDL-C, and triglycerides.
CCI [redacted]

See Appendix 8 for abbreviations.

2. INTRODUCTION

PF-06835919 is a ketohexokinase (KHK) inhibitor that is currently being investigated in participants with nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH).

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. In humans, Loss-of-function in KHK manifests as Essential Fructosuria, a rare, asymptomatic genetic condition[1] that 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. In nonclinical experiments, treatment with PF-06835919 reduces the incidence of fructose-induced hepatic steatosis and genetic deletion of KHK protects mice from fructose-induced hypertriglyceridemia, hyperinsulinemia, and hepatic steatosis (see investigators' brochure [IB] Section 5). Based on initial experience in short duration clinical trials, inhibition of KHK appears generally safe and well tolerated. In addition, PF-06835919 treatment has shown the potential to reduce liver fat and biomarkers of inflammation (see Section 2.2.2). It is anticipated that inhibition of KHK will decrease hepatic de novo lipogenesis and steatosis, thereby ameliorating the pathogenesis of NAFLD and its progression to NASH.

2.1. Study Rationale

The purpose of this study is to assess the safety and tolerability of PF-06835919 over a 16-week treatment period, as well as the effect of PF-06835919 treatment on liver fat, hemoglobin A1c (HbA1c), and additional pharmacodynamic (PD)/CCI parameters in participants with NAFLD and type 2 diabetes mellitus (T2DM).

2.2. 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 participants 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 participants 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 (TG) 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 the United States (US) population.[15] Risk factors for NASH include obesity, insulin resistance, T2DM, hypertension, and dyslipidemia, as manifested by low levels of high density lipoprotein cholesterol (HDL-C) and elevated TGs.

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.

2.2.1. Nonclinical Overview

In exploratory and/or pivotal toxicity studies conducted in rats and dogs, testes and ovary (rat), and the cardiovascular (rat, dog) and neuromuscular (dog) systems were identified as primary targets. Adverse findings identified in the pivotal toxicity studies in rats were degeneration of spermatids in seminiferous tubules of testes at ≥100 mg/kg/day (no-observed-adverse-effect level [NOAEL] = 30 mg/kg/day in the 6-month study, 2.8x the predicted human unbound area under the curve over 24 hours (AUC_{24}) at the highest planned clinical dose of 300 mg once daily [QD]), and an increased incidence (relative to controls) of decreased/absent corpora lutea in the ovary at ≥30 mg/kg/day (NOAEL = 10 mg/kg/day in

the 6-month study, 0.9x the predicted human unbound AUC_{24} at the highest planned clinical dose of 300 mg QD). The ovary finding was not observed in shorter term toxicity studies in rats at doses up to 175 mg/kg/day for up to 6 weeks (up to 8.2x the predicted human unbound AUC_{24} at the highest planned clinical dose of 300 mg QD). Increases in heart rate and blood pressure were noted at ≥20 mg/kg in safety pharmacology and general toxicology studies in dogs with a no-observed-effect level (NOEL) of 10 mg/kg and a margin of 1.5x the predicted human unbound maximum concentration (C_{max}) at the highest planned clinical dose of 300 mg QD. No PF-06835919-related arrhythmia or structural injuries to the heart or blood vessels were observed in any of the studies. Tremors were noted in earlier exploratory toxicity studies and in a single dog during the 6-week pivotal study in dogs, ranging from being mild and self-terminating at 50-60 mg/kg to being lasting and severe, with accompanying clinical signs (eg, ataxia, panting, rapid breathing), at doses up to and including a non-tolerated dose of 300 mg/kg. Tremors were seen at exposures representing 4.3-9.1x the predicted human unbound C_{max}, but convulsions were not seen at equivalent exposures in any study. PF-06835919 had an ultraviolet (UV) light absorbance but was negative in the in vitro phototoxicity assay, which indicates that it is not phototoxic and no further photosafety testing is recommended.

Although in vitro data indicated that PF-06835919 had the potential to induce CYP3A and CYP2B6 in humans at the highest planned clinical dose (300 mg QD), based on clinical drug-drug interaction (DDI) data (see Section 2.2.3), PF-06835919 does not appear to induce CYP3A4 at the highest dose administered in this study (300 mg QD). In addition, PF-06835919 has the potential to inhibit UGT1A1 and UGT1A4. Further, in vitro evaluations suggest that PF-06835919 has a low potential to inhibit intestinal P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), OAT3, OATP1B1, and OATP1B3.

The nonclinical safety profile of PF-06835919 has been adequately characterized to support clinical trials of up to 16 weeks.

2.2.2. Clinical Overview

As of February 2019, there are 3 completed sponsor-initiated clinical trials that administered PF-06835919 (C1061001, C1061002, and C1061003). Safety and tolerability findings from these studies are summarized below. In addition, a PF-06835919 midazolam DDI study (C1061016) is complete in the clinic and preliminary results are provided below.

The safety and tolerability of PF-06835919 has been assessed in 2 Phase 1 studies in healthy adults, C1061001 and C1061002. Across these 2 studies, 78 healthy adult participants (all males) were randomized, 68 (87%) were exposed to at least a single dose of PF-06835919, and 52 of these participants were exposed to repeated doses of PF-06835919. Single oral doses (up to 600 mg) and repeated daily doses (up to 330 mg) were found to be generally well tolerated with an acceptable safety profile. There were no treatment-emergent adverse events (TEAEs) of ‘severe’ intensity in the Phase 1 studies, and all of the TEAEs were ‘mild’ in intensity except for 4 ‘moderate’ intensity TEAEs (abdominal pain, rash, and 2 participants with headaches). The most frequently reported adverse event (AE) following multiple dose administration of PF-06835919 in Study C1061002 was headache (see IB Section 6.2).

In the Phase 2 C1061003 study, PF-06835919 was administered at QD doses of 75 mg, 300 mg, or placebo to adults with NAFLD over a 6-week period. The high dose of 300 mg QD was shown to reduce whole liver fat (18.7% linear, 21.5% log transformed) compared to placebo as assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF). Differences in liver fat between placebo and PF-06835919 at a dose of 75 mg were not statistically significant. In addition, favorable changes were observed for biomarkers of inflammation (high sensitivity C-reactive protein [hs-CRP]), insulin resistance (insulin and homeostatic model assessment of insulin resistance [HOMA-IR]) and markers of target engagement (uric acid and urinary fructose). Both dose levels were found to be generally well tolerated with an acceptable safety profile. In this study, a total of 14 (26.4%) participants reported 25 all-causality TEAEs during the study, with comparable AE rates observed across treatment groups (23.5-29.4%). One participant in the 300 mg group (5.9%) reported a severe TEAE of lower back pain, which was considered unrelated to study drug. One participant in the PF-06835919 300 mg group (5.9%) was withdrawn from the study due to a moderate TEAE of rash, and 1 participant in the placebo group (5.3%) was withdrawn from the study.

Of 102 subjects exposed to PF-06835919 in completed clinical studies to date (not including C1061016), there have been 2 reported TEAEs of hypoglycemia. These were mild in severity, and both were observed in the C1061001 Phase 1 (single ascending dose) study; 1 in a participant given 30 mg, and 1 in the 400 mg treatment group. There were no reported hypoglycemic AEs in the subsequent C1061002 Phase 1 (multiple ascending dose) study, or the C1061003 Phase 2a study.

Cumulatively, 131 adults have participated in PF-06835919 sponsor-initiated clinical trials worldwide, with 102 exposed to PF-06835919. In clinical trials to date, there have been no serious adverse events (SAEs) reported. There has been no clear, dose-related increase in the frequency of AEs with increasing doses of PF-06835919. Similarly, there have been no apparent adverse dose-related trends in analyses of safety laboratory abnormalities, electrocardiograms (ECGs), or vital signs.

2.2.3. Preliminary Pharmacokinetic Results of PF-06835919-Midazolam Drug-Drug Interaction Study (C1061016)

C1061016 was a Phase 1, randomized, open-label, 2-way crossover DDI study, which evaluated the impact of PF-06835919 on midazolam PK in healthy participants. CCI [redacted]

A total of 10 healthy adult participants were enrolled in this study. Preliminary results indicate that PF-06835919 was well tolerated in this study, and there were no new safety laboratory abnormalities, ECG, or vital sign changes of clinical concern when PF-06835919 was given concomitantly with midazolam, as compared with each agent alone.

Median plasma midazolam concentrations were similar following multiple doses of PF-06835919 compared to those observed for midazolam administered alone. Midazolam T_{max} values were similar between treatment periods (median T_{max} of 0.5 hours). Plasma concentrations declined in a monophasic manner with a similar mean terminal half-life ($t_{1/2}$) observed between the treatments: 5.267 hours for midazolam administered alone and 4.986 hours when administered with multiple doses of PF-06835919.

The statistical comparison of plasma concentrations of midazolam administered alone and with multiple doses of PF-06835919 are summarized in Table 1. The adjusted geometric mean for AUC_{inf} and C_{max} were similar, following co-administration with multiple doses of PF-06835919 as compared to midazolam administration alone. The ratio of the adjusted geometric means of midazolam AUC_{inf}, and C_{max} (90% confidence interval [CI]) were 97.55% (79.91%, 119.08%) and 98.92% (76.44%, 128.01%), respectively, following administration of midazolam with multiple doses of PF-06835919, relative to midazolam administered alone. Overall, these results indicate that there is no evidence of a meaningful effect of 300 mg PF-06835919 on CYP3A4.

Table 1. Statistical Summary of Effect of PF-06835919 on Plasma Midazolam PK Parameters (AUC_{inf}, AUC_{last} and C_{max}), Protocol C1061016

Statistical Summary of Effect of PF-06835919 on Plasma Midazolam PK Parameters (AUCinf, AUClast and Cmax), Protocol C1061016

	Adjusted Geometric Means			
Parameter (Unit)	PF-06835919 300mg + Midazolam 7.5mg (Test) N=10	Midazolam 7.5mg (Reference) N=10	Ratio (%) (Test/Reference) of Adjusted Geometric Means	90% CI for Ratio[a]
AUC_{inf} (ng.hr/mL)	127.6	130.8	97.55	(79.91, 119.08)
AUC_{last} (ng.hr/mL)	124.7	127.9	97.44	(80.20, 118.38)
C_{max} (ng/mL)	43.49	43.97	98.92	(76.44, 128.01)

Source: Table 14.4.5.2.1
Values had been back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
N: Total number of subjects in the treatment group and contributing to summary statistics.
a. The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 06AUG2019 (01:55) Source Data: adpp Output File: ./nda1_cdisc/C1061016/adpp_s102_i Date of Generation: 09AUG2019 (03:51)

2.3. Benefit/Risk Assessment

In completed clinical studies, PF-06835919 was determined to be well tolerated and to have an acceptable safety profile. There are no important identified risks for PF-06835919. The important potential risks for PF-06835919 identified in the nonclinical safety studies include ovarian changes, cardiovascular effects, tremors, and spermatid degeneration. In the ovary, an increased incidence (relative to controls) of decreased/absent corpora lutea was observed in female rats during the pivotal 6-month GLP toxicity study at doses similar to the higher dose levels anticipated for use in human studies (see Section 2.2.1). This was considered adverse due to the potential negative effect on the animal's fertility. However, these effects were not observed in rat studies up to 6 weeks duration, nor seen in any studies of

PF-06835919 in dogs up to 16 weeks. Based on available data, the effect of PF-06835919 on female ovaries and fertility is uncertain. As a precaution, women of child bearing potential (WOCBP) are excluded from this study.

Cardiovascular effects relate to an increase in heart rate seen at doses higher than those anticipated for human studies, which were considered non-adverse with no other correlating ECG, clinical or anatomic pathology findings, or impact to overall animal health. Tremors and spermatid degeneration were all observed at exposures higher than those tested in clinical studies. No adverse cardiovascular effects or tremors have been observed in clinical studies to date.

Based on Study C1061003, PF-06835919 administered at the 300 mg dose level was shown to reduce liver fat over a 6-week period. There have been no significant adverse clinical trends in laboratory values, vital signs, or changes in ECG parameters.

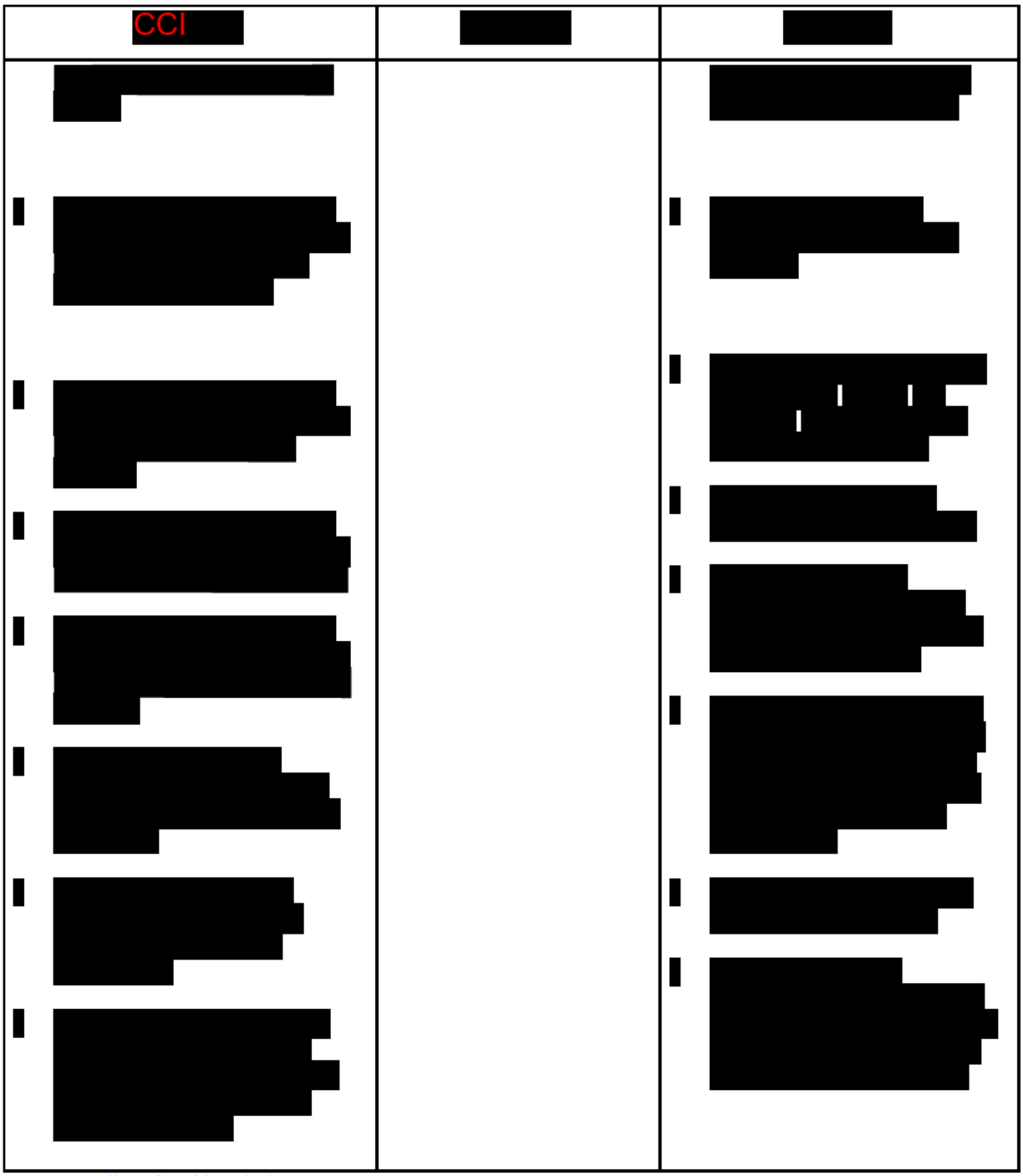
The sponsor considers that the available information about PF-06835919 from the non-clinical and clinical studies completed to date provides a favorable benefit-risk profile and supports the continued investigation of the compound as a potential treatment for NASH with liver fibrosis.

More detailed information about the known and expected benefits and risks, and reasonably expected AEs of PF-06835919 may be found in the IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To evaluate the effect of 2 dose levels of PF-06835919 compared to placebo on **whole liver fat** measured by MRI-PDFF. • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **HbA1c.**	• Estimand 1: • This estimand is intended to provide a population level estimate of the treatment effect of the IP alone relative to placebo under the scenario of no discontinuation of study intervention, without the potential confounding effects of additional prohibited medications, regardless of the participant's compliance with the IP dosing. Details in Section 9.1.1.	• %CFB in whole liver fat at 16 weeks using MRI-PDFF. • CFB in HbA1c at 16 weeks.

Objectives	Estimands	Endpoints
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the **safety and tolerability** of 2 dose levels of PF-06835919 administered daily for 16 weeks. • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **hs-CRP.** • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **glycemic metabolism.** • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **ALT.** • To evaluate the effects of 2 dose levels of PF-06835919 compared to placebo on **HbA1c.**	• No estimand is defined for safety and tolerability endpoints. These will be analyzed using Pfizer Data Standards, as applicable. • hs-CRP, measures of glycemic metabolism, ALT and HbA1c will be analyzed using Estimand 1.	• Assessment of AEs, including hypoglycemia AEs, clinical laboratory tests, vital signs and 12-lead ECGs. • %CFB in hs-CRP over 16 weeks. • CFB in fasting insulin, glucose, and HOMA-IR over 16 weeks. • %CFB in ALT over 16 weeks. • CFB in HbA1c at all time points other than Week 16.
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



See Appendix 8 for abbreviations.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, placebo-controlled, randomized, double-blind, parallel-group, multicenter study to evaluate the safety, tolerability, and PD of PF-06835919 administered QD for 16 weeks in adults with NAFLD and T2DM on stable doses of metformin.

A total of approximately 150 participants (50 per arm) will be randomized in a ratio of 1:1:1 between PF-06835919 at 150 mg and 300 mg, and placebo to ensure a minimum of approximately 132 participants (44 per arm) complete. The dropout rate for this study is presumed to be not more than approximately 12%.

For individual participants, the total duration of the study from the Screen 1 visit to the on-site follow-up visit (Visit 13) will be approximately 24 weeks. The time between Screen 1 (Visit 1) and Screen 3 (Visit 3) should be approximately 3 weeks, and approximately 6 weeks (42 days) between Screen 1 (Visit 1) and Day 1 (Visit 6).

In addition, a subset of participants across select sites in the US will be enrolled in an exploratory continuous data monitoring sub-study. Approximately 20 participants across select sites will be given 2 wearable devices: (1) a continuous glucose monitor (CGM) and (2) a wrist-worn, watch-like device containing, at a minimum, a heart rate monitor and accelerometer. The participants in this sub-study will have continuous data recorded via these devices during 2, up to 14-day time windows - once during run-in (starting at Visit 4) and once starting at Week 14. These participants will have 1 additional site visit at Week 14 (Visit 11) that is not required for any of the other study participants. For those sites participating in the sub-study, details and instructions regarding the wearable devices will be provided in writing prior to study start. This sub-study may be terminated following discussions with the sponsor. Completion of the trial will not be contingent on successful execution of the sub-study.

4.2. Scientific Rationale for Study Design

To determine the effects of PF-06835919 on HbA1c, this study will enroll adults with T2DM. In addition, to address the potential effect of PF-06835919 on liver fat, the eligible population for enrollment will be participants with NAFLD, defined as having liver fat ≥8%, as assessed by MRI-PDFF at Screen 3. FibroScan® assessments will be done at Visit 1 (Screen 1) and Visit 2 (Screen 2) to help initially estimate liver fat using a more efficient and scalable approach than MRI-PDFF. FibroScan® is an ultrasound based technique that estimates liver fat through calculation of a value referred to as the controlled attenuation parameter (CAP™) which is measured as decibels per meter (dB/m). CCI [redacted] The scan is performed on the right lobe of the liver through intercostal spaces via a transducer probe that delivers a painless, mechanical impulse to the liver and measures the resulting shear wave. The LSM is directly proportional to the velocity of the shear wave. Simultaneously, the CAP™ measures the ultrasonic attenuation coefficient in the forward and return path of the radio-frequency pulse through the liver. The

device calculates the median LSM and CAP™ values after a total of 10 valid, serial measurements are acquired per assessment. [redacted] If either CAP value at Screen 1 or Screen 2 is in the range of 260-279 dB/min, the measurement may be repeated, on a different day, following at least a 4-hour fast (except water).

Participants who meet all eligibility criteria for the study during Screen 1 (Visit 1; including liver fat approximation by FibroScan® at Screen 1 and Screen 2 (Visits 1 and 2, respectively) will then undergo liver fat assessment by MRI-PDFF. The MRI-PDFF technique is an established method that enables quantification of fat content in the liver. Imaging data are acquired with this method in a manner that accounts for confounding factors that can otherwise result in inaccurate measures of liver fat, while also providing whole-liver coverage such that fat content can be assessed across each of the 9 Couinaud liver segments. This noninvasive methodology has been found to be more sensitive to change in liver fat content than histologically-determined steatosis grade,[16] and has found utility in previous trials of prospective NASH therapeutics.[17,18]

MRI-PDFF assessments occur at baseline and after 16 weeks of investigational product (IP) administration to assess the integrated effects of study treatment on liver fat. No additional intermediate timepoints are planned for this study given the previous experience quantifying liver fat changes during a shorter duration 6-week study, C1061003. MRI-PDFF will also be assessed for any participants terminating from the study or discontinuing double-blind IP administration early, provided the early termination or IP discontinuation occurs at Week 8 (Visit 9) or beyond. This approach allows adequate assessment of PD response in participants while minimizing non-essential MRI scans in the early treatment period.

For the assessment of liver fat (either via FibroScan® or MRI-PDFF), participants will be required to fast (water permitted) for ≥4 hours given the ability of food to impact the results. An additional approach to limit measurement variability will be standardizing the nominal time for FibroScan® and MRI-PDFF assessments. Baseline assessments for MRI-PDFF and FibroScan® (Visits 5 and 6, respectively) should fall within a practical window (±2 hours) relative to clock time of the Screening visit for each assessment. All post-dose assessments for both MRI-PDFF and FibroScan® should occur within a practical window (±2 hours) relative to clock time of the baseline visit for each assessment (ie, Visits 5 and 6, respectively).

A fixed, single-blind, placebo run-in period of approximately 14 days following confirmation of eligibility and prior to randomization (ie, Visit 4 to Visit 6) is included to familiarize participants with the study treatment regimen and to exclude participants who are not compliant with single-blind placebo administration prior to randomization at Day 1 (Visit 6).

The 16-week duration of treatment chosen for this study is selected to permit sufficient characterization of the key primary and secondary metabolic endpoints. PF-06835919 was previously shown to reduce liver fat over 6 weeks of treatment, and this study will assess whether additional reductions are possible over an extended treatment period. In addition, glycemic biomarkers such as HbA1c and inflammatory biomarkers such as hs-CRP and alanine aminotransferase (ALT) typically require several months to accurately reflect metabolic changes. The total duration of dosing in this study is designed to capture these clinically pertinent metabolic changes and is supported by the completed nonclinical toxicity studies in rats and monkeys.

In this study, PF-06835919 administration will be requested to occur with the morning meal, given the importance of a morning meal to the standard-of-care diet counselling for the planned population, and because the expected mechanism of PF-06835919 is through inhibiting the metabolism of fructose consumed in the diet. CCI

This study is designed to assess the effect of PF-06835919 on liver fat, HbA1c, NASH-related PD markers, and other PD markers that are intended to provide insight into metabolic pathways distal to KHK inhibition. PD markers that are expected to be related to fructose metabolism include uric acid, TG, direct low-density lipoprotein cholesterol (LDL-C), HDL-C, total cholesterol, as well as the hormone insulin. Excess consumption of fructose has been linked to increased visceral adiposity, a hallmark of metabolic dysfunction and insulin resistance.[19] Fructose has also been suggested to induce hepatic oxidative stress and inflammation in a number of studies. Uric acid, a marker of oxidative stress is readily increased in humans following fructose consumption.[6] In this context, hs-CRP will be measured. Although this study is not specifically designed to assess the effects of PF-06835919 on chronic kidney disease, urine will also be collected to explore potential drug-related changes to albumin-to-creatinine ratio, a biomarker relevant to diabetic microvascular disease. CCI a calculated parameter using age, aspartate transaminase (AST), ALT and platelet count; CCI a calculated parameter using age, body mass index (BMI), ALT, AST, platelet count, albumin; CCI the N-terminal pro-peptide of type III procollagen which is a potential predictor of fast progressors and responders to therapy at baseline; CCI the C-terminal fragment of α3 chain of procollagen type VI (also known as Endotrophin) which is a potential predictor of responders to insulin sensitizers at baseline.

While no adverse trends in vital signs were observed in Phase 1 studies, an exposure-response analysis of the trough PK data from study C1061003 showed that, based on single measurements per time point, blood pressure (BP) increased and heart rate decreased with increasing exposure to PF-06835919. In C1061003, participants receiving PF-06835919 or placebo did not show meaningful BP changes at Week 6 compared to baseline, but participants who received placebo exhibited a modest pulse rate increase (approximately 5 beats per minute [bpm]) at Week 6 compared with baseline. In this study,

vital signs will be collected in triplicate CCI [redacted]

Hypoglycemia has been reported in 2 subjects given PF-06835919 in clinical studies performed to date; these were isolated to the C1061001 Phase 1 study, with no hypoglycemic AEs observed in the subsequent Phase 1 C1061002 multiple ascending dose study, or the C1061003 Phase 2a trial (see Section 2.2.2). Whilst the risk of hypoglycemia with PF-06835919 in the present study is considered low, blood glucose concentrations will be monitored at least 3 times weekly throughout the study via glucometer; and monitoring of symptomatic hypoglycemic AEs will be performed.

In a 6-month toxicology study in rats, changes in thyroid hormones were noted at doses ≥10 mg/kg/day. No thyroid findings were reported in any of the dog toxicity studies up to 9 months. Precautionary surveillance of thyroid hormone status (thyroid stimulating hormone [TSH] and thyroxine [T4]) will be measured in the current study at Week 0 and Week 16.

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.3. Justification for Dose

This study is planned as a 3-arm, parallel group study with 2 active PF-06835919 treatment arms (150 mg QD and 300 mg QD) and placebo to evaluate changes in liver fat and HbA1c in participants with elevated liver fat and T2DM.

In Study C1061003 where PF-06835919 or placebo was administered to participants with elevated liver fat, 300 mg was found to have been associated with a meaningful decrease in liver fat (approximate 20% reduction) while the lower dose of 75 mg was not significantly different than placebo. Both doses in C1061003 were generally well tolerated. The doses for this study were selected in order to further evaluate the effects of 300 mg (in a different population and for a longer duration) and to determine if a dose between those studied in C1061003 would be associated with meaningful improvement in liver fat and/or other PD markers being evaluated in this study. Notably, based on systems modeling based on data from the multiple ascending dose study in healthy participants (C1061002), KHK inhibition in the liver at the 300 mg dose is expected to be near maximal.

With the exception of a decreased/absent corpus lutea finding in the 6-month rat study (note: women of child-bearing potential [WOCBP] are excluded from this study), anticipated unbound exposures of PF-06835919 in this study are expected to provide sufficient margins over findings in the 6-month rat and 16-week dog toxicology studies (see Section 2.2.1). As exposures observed in the C1061002 study were approximately dose proportional, the anticipated exposure at the low dose (150 mg) is approximately half that of the high dose.

It is anticipated that the 300 mg dose of PF-06835919 administered in this study will have a similar effect on OATP substrates, as the 280 mg dose administered in Part B of the C1061002 study (see IB) which demonstrated an approximately 1.6-fold increase in atorvastatin AUC. Based on preliminary results of C1061016, PF-06835919 administered at the highest dose in this study (300 mg QD) has approximately no meaningful effect on plasma concentrations of a co-administered sensitive 3A4 substrate (midazolam). Based on these results, CYP3A4 substrates are allowed in this study. Specific concomitant medication exclusions are detailed in Section 6.5.

In summary, the 300 mg QD dose selected for this study is intended to fully assess the potential for KHK inhibition to reduce liver fat and HbA1c in adults with NAFLD and T2DM. The 150 mg dose was selected to explore if a dose between those that were previously shown to be effective (300 mg) and not effective (75 mg) in lowering liver fat in a previous 6-week study (C1061003) has potential for further clinical development.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the follow-up call (or visit, if required by investigator).

The end of the study is defined as the date of the last visit or follow-up phone call of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants 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 participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 70 years, inclusive, at Visit 1 (Screen 1). Females must be of non-childbearing potential.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Participants with T2DM on stable doses (≥500 mg/day) of metformin monotherapy for at least 8 weeks of Visit 1 (Screen 1).

4. At Visit 1 (Screen 1), waist circumference >102 centimeters for males and >89 centimeters for females with a maximum that allows for a subject to fit comfortably within the MRI machine.

5. At Visit 1 (Screen 1) and Visit 2 (Screen 2), a CAP™ ≥280 dB/m via FibroScan® assessment. If either CAP™ value is in the range of 260-279 dB/min, the measurement may be repeated, on a different day, following at least a 4-hour fast (except water).

6. At Visit 3 (Screen 3), liver fat ≥8% 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 8.1.1).

7. HbA1c at Screen 1 (Visit 1), as assessed by the sponsor-identified central laboratory of 7.0-10.5%, inclusive. Repeat assessments of HbA1c to determine study eligibility are NOT permitted.

Weight:

8. At Visit 1 (Screen 1), total body weight of >50 kg (kilograms; 110 lbs [pounds]) and a BMI of 25.0 – 40.0 kg/m^2, inclusive.

Informed Consent:

9. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Recent (ie, within 6 months prior to Screen 1) evidence or medical history of unstable concurrent disease such as: clinically significant hematological, endocrine, pulmonary, gastrointestinal (including severe gastroparesis), cardiovascular, hepatic, psychiatric, neurologic, or clinically significant allergic disease (including drug allergies, but excluding treated and untreated seasonal allergies at the time of dosing).

2. History or evidence of diabetic complications with significant end-organ damage, such as:

    - Proliferative retinopathy and/or macular edema; or diabetic neuropathy complicated by neuropathic ulcers or judged to be clinically significant as signified by need for chronic pharmacological intervention;

3. 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 participant inappropriate for entry into this study.

4. Participants 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, within 6 months of Screen 1 (Visit 1);

- 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 or defibrillators.

5. Participants 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 Screen 3 (Visit 3), by the sponsor-identified central imaging vendor, or participants 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;

    - Participants with metal implants, devices, paramagnetic objects contained within the body, and excessive or metal-containing tattoos;

    - Participants 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;

    - Participants with abdominal girth greater than the bore size of the site's MRI system.

Prior/Concomitant Therapy:

6. Refer to Section 6.5 for details regarding prohibited prior/concomitant therapies.

Prior/Concurrent Clinical Study Experience:

7. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of IP used in this study (whichever is longer).

8. Participants with known prior participation in a trial involving PF-06835919 (ie, received at least 1 dose of IP).

Diagnostic Assessments:

9. Fasting plasma glucose levels >270 mg/dL (15.0 mmol/L) at the Screen 1 (Visit 1) or run-in visit (Visit 4), as assessed by the sponsor-identified central laboratory and confirmed by a single repeat, if deemed necessary.

10. 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 ribonucleic acid (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 < lower limit of normal (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.

11. At Visit 1 (Screen 1), participants with an estimated glomerular filtration rate (GFR) <60 mL (milliliter)/min (minute)/1.73m2 as calculated by the modification of diet in renal disease equation (MDRD), and confirmed via a single repeat, if deemed necessary.

12. Participants with ANY of the following abnormalities in clinical laboratory tests at Screen 1 (Visit 1), as assessed by the sponsor-identified central laboratory and confirmed by a single repeat, if deemed necessary:

    - C-peptide concentration <0.8 ng/mL (267 pmol/L [picomoles per liter]);

- Fasting serum triglycerides ≥500 mg/dL (5.65 mmol/L);
- Fasting direct LDL-C >190 mg/dL (4.92 mmol/L);
- AST or ALT ≥2.0x upper limit of normal (ULN);
- Total bilirubin ≥1.5x ULN **and** direct bilirubin ≥ULN.

13. Seated systolic BP >160 mmHg and/or diastolic BP >100 mmHg after at least a 5-minute rest at Screen 1 (Visit 1). BP is determined as the mean of triplicate measurements collected with 2-4 minutes of rest between measurements.

14. At Screen 1 (Visit 1), standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT [QTcF] interval >450 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

15. A positive urine drug test for potential drugs of abuse at Screen 1 (Visit 1), including medical marijuana. Participants that have been medically prescribed opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at Screen 1 (Visit 1) may be allowed to participate if approved by the sponsor.

Other Exclusions:

16. Compliance of <90% (based on pill count) during the 2-week, single-blind run-in period, as assessed prior to randomization on Day 1 (ie, participants cannot miss more than 1 dose).

17. History (within the last 6 months) of regular alcohol consumption exceeding 21 drinks per week for men and 14 drinks a week for women (1 drink = 5 ounces of wine (150 mL) or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor).

18. Male participants with partners who are currently pregnant; or male participants able to father children and are unwilling or unable to use a highly effective method of contraception for the duration of the study and for at least 5 days after the last dose of IP.

19. Participation in a formal weight loss program or use of agents suspected to cause weight loss within 3 months prior to Visit 1 (Screen 1).

20. Weight loss of ≥5% within 1 month prior to Visit 1 (Screen 1).

21. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to randomization on Day 1 (Visit 6).

22. 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 Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants 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 participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant's partner.

5.3.2. Dietary Restrictions

- Participants must abstain from all food and drink (except water) for **≥8 hours** prior to any blood sample collections for clinical laboratory tests, fasting glucose monitoring, CCI
- Water may be consumed as desired (ad libitum);
- Blinded IP must be administered every day with the morning meal;
- On scheduled outpatient visits to the site, ***in the morning***, from Visit 4 (Day -14) through Visit 12 (Week 16), participants must be instructed to arrive **without** having morning meal/breakfast, self-administration of the blinded IP, *and* morning dose of allowed concomitant medication(s), if applicable, for the given day;
    - At Visit 4 (Day -14) through Visit 12 (Week 16), inclusive, the morning meal will be consumed with above-mentioned medications at the site [with the meal *either* provided by the site, *or* the participant provided a voucher (or similar) by the site to purchase the meal before arriving at the site for each visit].
- Each outpatient visit to the imaging facility (for MRI-PDFF) will occur following a fast (water permitted) of ≥4 hours;
- For assessment via FibroScan®, visits will occur following a fast (water permitted) of ≥4 hours;

- Participants will be counseled on appropriate dietary and lifestyle guidelines, at Visit 4 (Run-in/Day -14) and again at Visit 6 (Day 1):
  - Participants will be asked to maintain these guidelines throughout the study (ie, Visit 13, the on-site Follow-up);
  - Counseling on dietary guidelines should be individualized in accordance with local medical standards of care for these patients and appropriate for the concomitant medical condition(s) of each participant.

5.3.3. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted in moderation (refer to Exclusion Criterion for limits on amount of alcohol consumption);
- 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. In addition, consumption is ***prohibited*** for at least 1 hour prior to any vital sign measurement.

5.3.4. Activity

- Participants will **not** be permitted to engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within **48 hours** before each blood sample collection for clinical laboratory tests for the duration of participation in the study; physical activity at an individual subject's normal pace is permitted.

5.3.5. Confinement to Site

- Each outpatient visit to the site will occur *with the subject arriving at the site* between approximately 6 AM and 10 AM with each visit to last approximately 2 hours – CCI [redacted]
- Visit to the imaging facility for MRI-PDFF (± FibroScan®) assessment will have restrictions related to prior meals/food consumption and clock time of day (see SoA).

5.3.6. Confinement at Imaging Facility

- Each outpatient visit to the imaging facility (for MRI-PDFF) will occur at the same time of day (±2 hours) relative to MRI-PDFF completed at Visit 3 (Screen 3); refer to Section 8.1 or additional details;
- For assessment via FibroScan®, visits will occur either to the site **or** the imaging facility, depending on where the FibroScan® device is located. However, the location of the device must be kept consistent at individual sites throughout study execution;

- Similar to MRI-PDFF, each assessment via FibroScan® to occur at the same time of day (±2 hours) relative to FibroScan® assessment completed at Visit 1 (Screen 1).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to investigational product. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who were considered screen failures may be rescreened only after a discussion with the sponsor. If rescreened, these participants should be assigned a different participant number from the initial screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term IP may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06835919	Placebo for PF-06835919
ARM Name	Active	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	Mg	mg
Dosage Level(s)	150 or 300, QD	0, QD
Route of Administration	Oral	Oral
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to IP Manual for further information.	Provided centrally by the sponsor. Refer to IP Manual for further information.
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled in blinded fashion as required per country requirement.	Study intervention will be provided in bottles. Each bottle will be labeled in blinded fashion as required per country requirement.

6.1.1. Administration

Participants will swallow the IP whole and will not manipulate or chew the IP prior to swallowing.

To maintain the blind, administration of IP will use a strategy so that all participants will receive an equal number of tablets, regardless of which dose they are assigned. Tablets will be active drug (50 mg or 100 mg) or placebo.

Participants 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. Dosing will be witnessed by the investigator site staff at Visit 4, and Visits 6, 7, 8, 9,10, and 12. Participants will be instructed to delay self-administration of IP and concomitant medications on scheduled visit days until they arrive for their outpatient clinic visit, except participants in the sub-study at their Week 14 (Visit 11). At visits when participants report to the imaging center, dosing and breakfast should be delayed until completion of the MRI-PDFF procedure.

Participants 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 participant remembers missing a dose the next day or later, they should be instructed NOT to take 2 doses in the same day.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an IP accountability form/record. All empty containers should be returned to the site at each visit when drug accountability will be performed.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual or other specified location.

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

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (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.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

Participants will be assigned a subject identification number using an interactive response technology (IRT) drug management system. The IP will be dispensed using IRT at each visit from Visit 4 (single-blind) to Visit 10 (double-blind), excluding Visits 5 and 11 (Note: Visit 11 applicable *only* to participants in the substudy). A qualified staff member will dispense the IP via unique container numbers in the bottles provided, in quantities appropriate for the study visit schedule. The participant should be instructed to maintain the product in the bottles provided throughout the course of dosing and return the bottles to the site at the next study visit. Dosing instructions will be provided to the sites and individual participants. Upon receipt of the new bottle, the used bottle will be returned. Participants will be instructed to store the study drug at room temperature and out of the reach of small children.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Allocation of participants to treatment groups will proceed through the use of an 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 participant 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 participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

IP will be dispensed at the study visits summarized in the SoA.

Returned IP must not be redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF).

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Compliance of single-blind placebo administration during the run-in period will be assessed by pill count on Day 1 (Visit 6) for the purpose of inclusion into the study. Acceptable compliance will be defined as self-administration by the participants of:

- ≥90% of the study-supplied blinded placebo taken by the participant during the run-in period (ie, Visit 4 to Visit 5) - only 1 dose is permitted to be missed.

Compliance of IP administration will be assessed during the treatment phase of the study by the number of tablets returned by the participants at Visits 7, 8, 9, 10, and 12.

- >80% compliance with self-administration of the IP is expected from Day 1 (Visit 6) to Day 112 (Visit 12); investigators must closely monitor non-compliant participants in order to enhance their adherence to the study treatment.

At Visit 4 (run-in), participants will be provided with a dosing diary (or similar) and instructed on how to record each dose taken throughout the study through Visit 12 (Week 16). Participants will bring the dosing diary to each clinic visit to be reviewed by clinic staff.

6.5. Concomitant Therapy

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 communicated to the sponsor's medical monitor as soon as practically possible, and if agreed, be captured in the CRF. All participants must be questioned about concomitant medication at each outpatient visit to the clinical site.

Medications taken before Visit 6 (Day 1) will be documented as prior medications. Medications taken after dosing of double-blind IP at Visit 6 (Day 1) and until the second Follow-up (telephone contact or visit) will be documented as concomitant medications.

Medications for Glycemic Control

Participants must be on a stable dose of **metformin (≥500 mg /day)** starting at ≥**8 weeks prior to Visit 1 (Screen 1)** and until Visit 13 (on-site Follow-up).

The use of the following classes of agents is **not** permitted within **8 weeks** prior to Visit 1 (Screen 1) and until Visit 13 (on-site Follow-up):

- Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone;
- Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, pramlintide);
- Sodium-glucose co-transporter 2 inhibitors such as canagliflozin, dapagliflozin, empagliflozin;
- Sulfonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamine, glimepiride, glipizide, glyburide;
- Meglitinide analogues such as repaglinide, nateglinide;
- Dipeptidyl peptidase-4 inhibitors (DPP-4i) such as sitagliptin, saxagliptin, linagliptin, vildagliptin; or
- α glucosidase inhibitors such as acarbose and miglitol.

Lipid-modifying Medications

Use of background lipid-modifying agent(s) are permitted unless otherwise specified in this protocol. If possible, doses of lipid modifying agents should be stable for **≥4 weeks** prior to Visit 1 (Screen 1) and for the duration of the study. Any changes to dose of lipid modifying agents should be noted on the CRF.

Participants are permitted to be on stable doses of the following lipid-modifying agents, starting at ≥**4 weeks** prior to Visit 1 (Screen 1) and until Visit 13 (on-site Follow-up), including (but not limited to) the following:

- Statins such as atorvastatin, simvastatin, rosuvastatin, fluvastatin, pitavastatin, and pravastatin;
- Ezetimibe.

The following lipid-modifying agents are not permitted in this study within **4 weeks** prior to Visit 1 (Screen 1) and for the duration of the study:

- Bile acid sequestrants such as cholestyramine, colestipol, colesevalam;
- Fenofibrate and gemfobrozil;
- Nicotinic acid/niacin; or
- Monoclonal antibodies inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9), such as alirocumab and evolocumab.

Antihypertensive Medications

Use of background antihypertensive agent(s) is permitted unless otherwise specified in this protocol.

For participants that enter the study taking allowable antihypertensive agents, doses should be stable for **≥4 weeks** prior to Visit 1 (Screen 1) and for the duration of the study. Any changes to dose of blood pressure modifying agents should be avoided if possible; however, if any changes occur, they must be noted on the CRF.

Other Acceptable Concomitant Medications

Any participant on the following list of medications must be on stable doses [ie, **≥8 weeks** prior to Visit 1 (Screen 1) and until Visit 13 (on-site Follow-up), if possible]:

- Non-steroidal anti-inflammatory drugs (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 females);
- Anti-psychotic medications such as olanzapine and risperidone;
- Antidepressant medications such as tricyclic agents, selective serotonin reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors;
- Vitamin E, including high doses provided 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.

Other Prohibited Concomitant Medications

Participants must abstain from using the following medications for **≥4 weeks** prior to Visit 1 (Screen 1) and until Visit 13 (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 including:
  - Coumadin-type anticoagulants *or* other anticoagulants (eg, dabigatran); *though* aspirin at doses ≤325 mg/day is permitted;
  - Anticonvulsants; or

- Antiarrhythmics, except for beta blockers if used for the management of conditions other than arrhythmias (eg, blood pressure control);

- Medications historically associated with fatty liver are prohibited if used for **≥4 weeks of continuous use** in the previous 13 months prior to Screen 1 (Visit 1), examples include:

  - Amiodarone, methotrexate, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, or other known hepatotoxins.

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06835919; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

No dose modifications are permitted in this study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue IP. Also, it should be stressed that if the study medication is discontinued for any reason, it is fully anticipated that subjects continue in the study per protocol (Off Drug In Study or ODIS) per treatment policy estimand. Should the ODIS subject withdraw from the study, an Early Termination Visit should be scheduled at the time consent is withdrawn and evaluated for early termination procedures as listed in the SoA.

ECG Changes

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study.

- QTcF >500 msec;

- Change from baseline (CFB): QTcF >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new, clinically relevant finding should be reported as an AE.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request (and choose not to continue as an ODIS subject) or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants 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 participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants 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 participant 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.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

The total blood sampling volume for individual participants in this study is approximately 230 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

8.1.1. Imaging Assessments

[redacted]

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

At scheduled visits (refer to the SoA), liver fat 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 those 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 provided to the sites prior to the start of the study.

As much as practically possible, analysis of the MRI-PDFF images acquired from baseline (Visit 5) to Visit 12 (Week 16) will be undertaken by a single colleague at the sponsor-identified central imaging vendor who will be blinded to individual participant's clinical data, as well as randomization assignment.

CCI [redacted]

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

A participant's eligibility for this study based on liver fat as assessed via MRI-PDFF at Screen 3 (Visit 3) will be made by the sponsor-identified central imaging vendor only. The individual participant's liver fat will not be communicated. In the case of the MRI at Screen 3 (Visit 3), study sites will only be informed whether a participant 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, participants 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.

Management of Incidental Findings

An incidental finding is one unknown to the participant 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 MRI images will be reviewed by a 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 participant. 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 (PI). All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting

section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

A complete physical examination will occur at times specified in the SoA and include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at Screen 1 only) and weight will also be measured and recorded.

A limited physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.1.1. 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 participant 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.

8.2.2. Body Weight

In this study, assessment of body weight will occur at the nominal time points specified in the SoA 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 participant has been asked to void (ie, forced void);
  - Under standard conditions (eg, participants must wear light clothing with content of their pockets emptied or hospital gown **and not** be wearing shoes or bulky layers of clothing/jackets).

8.2.3. Vital Signs

Pulse rate and BP will be assessed in triplicate (2-4 minutes between measurements) at times specified in the SoA section of this protocol per the following specifications:

- At Screen 1 (Visit 1) only, the participant'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);
  - Participants 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 participant's arm supported at the level of the heart, and recorded to the nearest mmHg, following a rest of **≥5 minutes**;
- The same arm (preferably the dominant arm) will be used for BP/pulse rate assessment throughout the study;
- Participants 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.

8.2.4. Electrocardiograms

Standard 12-lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures pulse rate, QT, and QTcF intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for **≥10 minutes** in a supine position.

If a postdose QTcF interval remains ≥30 msec from the baseline **and** is >450 msec; or an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

ECG values of potential clinical concern are listed in Appendix 7.

8.2.5. Clinical Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5.1. Management of Glycemic Control

Hypoglycemic adverse events (HAEs) and fasting plasma glucose will be routinely monitored during participation in the study.

Based on this information, as well as review of the results reported by the central laboratory, an assessment of any symptomatic and asymptomatic occurrence of hypo- or hyper-glycemia must be undertaken.

8.2.5.1.1. Home Glucose Monitoring

- To aide in management of their T2DM, all participants will be provided home glucose monitoring supplies including a sponsor-provided glucometer, instructions on the use of the glucometer and accompanying supplies.

- Home glucose monitoring logs will be provided to participants for completion at home and brought to each outpatient visit to the site along with the glucometers. Investigators must review the home glucose monitoring logs completed by the participants and the readings stored in the glucometer device at each visit to the site after the run-in visit (Visit 4).

- Participants must perform home glucose monitoring **at least 3 times weekly** following at least an 8- (preferably 10-) hour fast (except water). However, the investigator may recommend more frequent home glucose monitoring if needed.

- Less frequent glucose monitoring will NOT be considered a protocol deviation unless the participant fails to monitor his/her glucose for 3 or more consecutive days.

- If the participant experiences symptoms of hypoglycemia, home glucose monitoring should be performed, and these symptoms, along with the glucometer measurement, should be captured on the home glucose monitoring log.

- If the participant uses his/her own glucometer, and not one provided by the sponsor, a protocol deviation will NOT be recorded provided the investigator is still able to monitor the participant's daily glucose values according to the criteria stated above.

8.2.5.1.2. Management of Hypoglycemia

Any episode of hypoglycemia must be captured on the Hypoglycemia Adverse Event CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.2.5.1.2.1 below.

Participants noted to have a fasting plasma glucose value (during home glucose monitoring) meeting the definition of hypoglycemia must be instructed to repeat the measurement the next day (following at least an 8- (preferably 10-) hour fast, except water). If the second measurement also meets the below definition, participants must be asked to return to the site within 1 to 3 days (following at least an 8- (preferably 10-) hour fast, except water) and have blood collected and sent to the central laboratory for analysis of fasting plasma glucose.

8.2.5.1.2.1. Definition and Severity of Categorization of Hypoglycemic Adverse Event (HAE)

Based on review of the participant completed home glucose monitoring log at each site visit, as well as results reported by the central laboratory, the investigator must assess the glucose values as well as any symptoms documented.

HAE is defined as **1** of the following:

1. **Asymptomatic hypoglycemia:** An event *not* accompanied by typical symptoms of HAE but a plasma glucose value of <70 mg/dL (3.9 mmol/L) using glucometer (or sponsor-identified central laboratory);

2. Documented symptomatic hypoglycemia: An event during which typical symptoms of HAE are accompanied with a glucose value of <70 mg/dL (3.9 mmol/L) using glucometer (or sponsor-identified central laboratory) and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or intravenous (IV) glucose;

3. Probable symptomatic hypoglycemia: An event during which symptoms of HAE are not accompanied by a plasma glucose determination but was presumably caused by a plasma glucose concentration of <70 mg/dL (3.9 mmol/L), and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or IV glucose.

Each episode of HAE must be categorized with respect to severity. In order to characterize the event as severe, all **3** criteria below must be met:

1. The participant was unable to treat him/herself. Neurologic impairment, and not the age of the participant, is the explanation for why the participant could not treat him/herself and required the assistance of another person.

2. The participant exhibited at least one of the following neurological symptoms:

    - Memory loss;
    - Confusion;
    - Uncontrolled behavior;
    - Irrational behavior;

- Unusual difficulty in awakening;
- Suspected seizure;
- Seizure;
- Loss of consciousness.

3. Either:
   - If blood glucose was measured and was ≤54 mg/dL (2.7 mmol/L) using glucometer (or central laboratory); or
   - If blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

Events that do not meet all the criteria above for severe HAE are characterized as mild or moderate in severity.

Any episode of HAE must be captured on the HAE CRF.

8.2.5.1.3. Management of Hyperglycemia

Hyperglycemia is defined as the following:

- Fasting plasma glucose ≥270 mg/dL (15.0 mmol/L) using glucometer (or central laboratory).

After randomization, participants noted to have a fasting plasma glucose value (during home glucose monitoring) meeting the above definition of hyperglycemia must be instructed to repeat the measurement the next day (following at least an 8- (preferably 10-) hour fast, except water). If the second measurement also meets the above definition, participants must be asked to return to the site a day later (following at least an 8- (preferably 10-) hour fast, except water) and have blood collected for fasting plasma glucose (and shipped to the central laboratory for analysis).

The investigator should determine if the participant collected the samples after an adequate fasting period; and if the participant is following recommended dietary guidelines. Proper dietary and collected procedures should be reinforced with the participant.

If the results from the central laboratory confirm the readings using glucometer, the participant should receive glycemic rescue medication at the discretion of the investigator (see Section 6.5.1).

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant'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, except as indicated below.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

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.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant 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 investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure 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.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until 28 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. 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.

8.3.5.3. 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 participant 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.

8.3.6. Medication Errors

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

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

Medication errors include:

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

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 nonserious, 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.**

8.4. Treatment of Overdose

For this study, any dose of PF-06835919 greater than 600 mg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until PF-06835919 can no longer be detected systemically (at least 5 days).

CCI [redacted]

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

CCI [redacted]

CCI [redacted]

[redacted]

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

[redacted]

8.6. Pharmacodynamics

Blood and urine samples to provide the required volume for analysis, will be collected and processed for measurements outlined below at times specified in the SoA.

Samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical study report (CSR).

Samples will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs).

These samples will be processed and shipped for analysis to the sponsor-identified central laboratory to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.6.1. Glucose, Insulin, and HbA1c

Fasting plasma glucose will be collected as part of the clinical laboratory tests. In addition, a sufficient amount of blood will be collected for analysis of plasma insulin and HbA1c.

HOMA-IR values will be derived from fasting plasma insulin and glucose values which will be described in the Statistical Analysis Plan (SAP).

8.6.2. Lipid Panel

Blood will be collected for analysis of serum triglycerides, total cholesterol, direct LDL-C, and HDL-C. Non-HDL-C values will be derived from other lipid parameter values which will be described in the SAP.

8.6.3. Urine for Albumin-to-Creatinine Ratio

Urine samples will be collected for analysis of the ratio of albumin to creatinine.

8.6.4. hs-CRP

Approximately 2.5 mL of blood will be collected to ensure sufficient serum for analysis of hs-CRP. These samples will be processed and shipped for analysis to the sponsor-identified central laboratory.

CCI [redacted]

The exploratory collection for these markers, *if analyzed*, will be reported separately and not included in the CSR.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

8.8. Biomarkers

Collection of samples for biomarker research are also part of this study.

8.8.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

CCI

[redacted]

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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. Estimands and Statistical Hypotheses

The hypothesis of no difference between each PF-06835919 dose and placebo will be tested for each primary and selected secondary and tertiary endpoints. The alternative hypothesis would confirm the sufficiency of evidence otherwise.

9.1.1. Estimands

Two estimands are defined for this study. Estimand 1 will be used to support all primary, secondary and tertiary objectives. Estimand 2 will be the treatment policy estimand used to support the exploratory objective of assessing the robustness of the effect of primary endpoints.

Estimand 1:

Estimand 1 is intended to provide a population level estimate of the treatment effect of the IP alone relative to placebo under the scenario of no discontinuation of study intervention, without the potential confounding effects of additional prohibited medications, regardless of the participant's compliance with the IP dosing.

Population:

The target population consists of patients with NAFLD and T2DM on stable doses (≥500 mg/day) of metformin monotherapy.

Intercurrent Events:

a. Withdrawal from study intervention – All data collected after a participant stops taking study medication will be excluded.

b. Prohibited medications – All assessments after a participant receives prohibited medications that would modulate the primary endpoints will be omitted from the analysis. Receiving a medication prohibited due to drug-drug interaction (DDI) risk will not affect this estimand. The list of concomitant medications would be reviewed prior to database lock to determine which would be classed as "prohibited" for this estimand.

c. Inadequate compliance – Participants with inadequate compliance will have their primary endpoint measurements used as recorded in the analysis.

Population level summary:

The population level summary will be the mean difference in change from baseline between PF-06835919 and placebo arms for the endpoint of interest.

Estimand 2:

Estimand 2 is intended to provide a population level estimate of the treatment effect of the IP alone relative to placebo on liver fat measured by MRI-PDFF and HbA1c at Week 16 without regard to compliance or discontinuation of study drug or administration of prohibited medication.

Population:

- The target population consists of patients with NAFLD and T2DM on stable doses (≥500 mg/day) of metformin monotherapy.

Intercurrent Events:

a. Withdrawal from study intervention – All data collected regardless of a participant's withdrawal from the study medication will be included in the analysis.

b. Prohibited medications – All data collected for a participant regardless of the use of prohibited medications will be used in the analysis.

c. Inadequate compliance – Participants with inadequate compliance will have their primary endpoint measurements used as recorded in the analysis.

Population level summary:

The population level summary will be the mean difference in change from baseline between PF-06835919 and placebo arms for the endpoint of interest.

9.2. Sample Size Determination

A sufficient number of participants will be screened to achieve approximately 150 participants randomly assigned to IP and an estimated total of 50 evaluable participants per intervention group. A maximum of approximately 150 participants will be randomly assigned to IP such that approximately 132 evaluable participants complete the study.

This assumes an approximate 12% dropout rate resulting in 44 completers per arm. With this sample size, the power to detect a 25% mean reduction in whole liver fat from MRI-PDFF compared to placebo is 98% 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) of 0.36 in the log-scale (based on an internal study). For the co-primary endpoint of HbA1c, the power to detect a 0.75% mean reduction compared to placebo is 96% using a 2-sample t-test and a 2-sided Type I error rate of 0.1 assuming a pooled SD of 1%. There will not be any adjustment for multiplicity in the assessment of hypotheses for the 2 co-primary endpoints.

The number of participants in the sub-study will be recruited based on feasibility.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Pre-randomization	All participants entering the placebo run-in phase.
Randomly assigned to Treatment	Defined according to Full Analysis Set.
Safety	All participants randomly assigned to treatment and who take at least 1 dose of treatment. Participants will be analyzed according to the dose they actually received.

Defined Population for Analysis	Description
Full Analysis Set	All participants randomly assigned to treatment and who take at least 1 dose of treatment.
CCI [redacted]	[redacted]

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	**1. Whole Liver Fat Using MRI-PDFF** Here the %CFB at Week 16 will be the derived endpoint. Baseline will be the measurement obtained at Visit 6 prior to randomization. Analysis of covariance (ANCOVA) will be performed on log-transformed CFB with treatment and log-transformed baseline whole liver PDFF value as covariates. Estimates of the mean relative differences between each active dose and placebo at Week 16 and the corresponding 90% confidence interval (CI) will be obtained from the model to estimate the effect of the initially randomized treatment regardless of treatment compliance. Comparison of each PF-06835919 dose with the placebo will be performed at a Type I error rate of 10% (2-sided). No adjustment for multiple comparisons will be made. This analysis will utilize the Full Analysis Set. Descriptive summaries of the observed values and %CFB in whole liver PDFF for each treatment group will also be produced. **2. HbA1c** Here the CFB at post-baseline visits will be the derived endpoint. Baseline will be the closest measurement prior to first dose on Day 1. Analysis using mixed model with repeated measures (MMRM) will be performed on CFB with treatment, time and treatment by time interaction as fixed effects and baseline HbA1c value as a covariate. Time will be fitted as a repeated effect. Estimates of the mean differences between each active dose and placebo at all post-baseline time points including the primary time point of Week 16 and the

Endpoint	Statistical Analysis Methods
	corresponding 90% CIs will be obtained from the model to estimate the effect of the initially randomized treatment regardless of treatment compliance. Comparison of each PF-06835919 dose with the placebo will be performed at a Type I error rate of 10% (2-sided). No adjustment for multiple comparisons will be made. This analysis will utilize the Full Analysis Set. Descriptive summaries of the observed values and CFB in HbA1c for each treatment group at each time point will also be produced.
Secondary	**hs-CRP, Measures of Glucose Metabolism, ALT** For hs-CRP and ALT the derived endpoint will be the %CFB. For measures of glycemic metabolism namely, fasting plasma glucose, fasting plasma insulin, and HOMA-IR the derived endpoint will be the CFB. Baseline will be the closest measurement prior to first dose on Day 1. The derived endpoints will be analyzed using MMRM with treatment, time and treatment by time interaction as fixed effects and baseline value as a covariate. Additional covariates, if considered for inclusion in the model, will be described in the SAP. If the MMRM does not fit the data then group medians and differences in group medians from placebo with 90% CIs will be provided at each post-baseline time point to estimate the effect of the initially randomized treatment regardless of treatment compliance. This analysis will utilize the Full Analysis Set.
CCI [redacted]	[redacted]

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Secondary	The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include: • TEAEs including hypoglyceimic AEs and SAEs; • Withdrawals from active treatment due to AEs; • Safety laboratory tests;

Endpoint	Statistical Analysis Methods
	• Vital signs; • ECGs.
CCI [redacted]	[redacted]

9.4.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with corrected and uncorrected QT values >500 msec will be summarized.

CCI [redacted]

9.5. Interim Analyses

Interim analyses may be performed to assess efficacy or/and safety after at least 30% of the planned participants (ie, approximately 45 participants), complete their study participation through the end of the treatment phase of the study (ie, Week 16). Interim analysis results may be used for internal business decisions including, but not limited to, future study planning, stopping for futility, stopping for early success, conducting a sample size re-estimation, or adapting the study after the interim analysis. Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an internal review committee (IRC) charter. In addition, the analysis details must be documented and approved in an interim analysis SAP or final SAP.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC). This study will use an IRC. The IRC will be responsible for ongoing monitoring of safety of participants in the study according to the charter. Members of the IRC will be qualified and experienced in

reviewing and interpreting clinical study data. They will be external to and independent of the study team, and unblinded to treatment. The recommendations made by the IRC to alter the conduct of the study will be forwarded to Pfizer Leadership for final decision. This will not include the members of the study team. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Pfizer may perform an interim analysis as described in Section 9.5 which may include safety and efficacy data. If an interim analysis is performed, the same IRC will be used. Details of the IRC will be described in the IRC charter.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;

- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;

- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;

- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. 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 investigational product, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study 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 addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

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 product, regardless of the geographical location in which the study is conducted. US Basic Results are generally 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 participant 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 (CSR synopses in which any data that could be used to identify individual participants have 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.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of “bona-fide scientific research” that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor 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 participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. 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 team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant 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 participant'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 participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following clinical laboratory tests will be performed at times defined in the SoA section of this protocol. 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 laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

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	Coagulation: PT, INR, aPTT[b] Serum FSH (females)[b] Urine drug test[b,c] Serology: HBsAg, HCV Ab (and if positive, reflex HCV RNA), HIV[b] HbA1c A1AT[b] Ceruloplasmin[b] Thyroid panel[d] CCI
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. At Screen 1 (Visit 1) only.
c. Minimum requirement for urine drug test include cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.
d. At Day 1 (Visit 6) and Day 112 (Visit 12) and early termination. Thyroid panel includes TSH, and free T4.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded are as follows: HbA1c, insulin, hs-CRP, uric acid, and GGT.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse 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) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

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.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. 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.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 5 days after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception is required for WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

- A female participant is eligible to participate if she is not a WOCBP (see definitions below in Section 10.4.3).

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

   - Documented bilateral salpingectomy;

   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods

The following apply to WOCBP partners of male participants:

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;
    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Collection of Pregnancy Information

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 investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - 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 investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, 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 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 preprocedure 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 investigational product.

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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

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10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants 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 laboratory 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 participant’s individual baseline values and underlying conditions. Participants 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:

- Participants 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 participants 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 participant 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 for suspected cases of Hy's law, additional 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, and alkaline phosphatase. 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) and collection of serum sample for acetaminophen drug and/or protein adduct levels 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 liver function test (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.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  - In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Abbreviations

The 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
AUC24	systemic exposure over 24 hours
AUEC24	area under the effect curve over 24 hours
AV	atrioventricular
CCI	[redacted]
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CAP	controlled attenuation parameter
CFB	change from baseline
CFR	Code of Federal Regulations
CGM	continuous glucose monitor
ChREBP	carbohydrate-responsive element-binding protein
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CCI	[redacted]
CK	creatine kinase
CLp	plasma clearance
Cmax	maximum concentration
CO2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSA	clinical study agreement

Abbreviation	Term
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
dL	deciliter
DMC	data monitoring committee
CCI	[redacted]
DPP-4i	dipeptidyl peptidase-4 inhibitors
DU	dispensable unit
EC50	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
Emax	efficacy
EU	European Union
EudraCT	European Clinical Trials Database
F1P	fructose-1-phosphate
F	bioavailability
FIH	first in human
FSH	follicle-stimulating hormone
fu	unbound plasma fraction
F/U	Follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GLP-1r	glucagon-like peptide 1 receptor
HAE(s)	hypoglycemia adverse event(s)
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

Abbreviation	Term
HEK	human embryonic kidney
HepB	hepatitis B
HepC	hepatitis C
hERG	human Ether-a-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IC50	50% of the inhibition concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IDL	intermediate-density lipoprotein
IL-6	interleukin 6
IMP	Investigational Medicinal Product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISAP	interim statistical analysis plan
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWR	interactive web response
K2EDTA	dipotassium ethylenediaminetetraacetic acid
kg	kilogram
KHK	ketohexokinase
Ki	inhibitory constant
kPa	kilopascals
LBBB	left bundle branch block
lbs	pounds
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
LFT	liver function test
LSLV	last subject last visit
LSM	liver stiffness measure
m2	meter squared
MAR	missing at random
max	maximum
MCH	mean corpuscular hemoglobin

Abbreviation	Term
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MELD	model of end-stage liver disease
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters of mercury
mmol/L	millimoles per liter
MMRM	mixed model with repeated measures
MOA	mechanism of action
MRI	magnetic resonance imaging
msec	millisecond
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
ND	not determined
ng	nanograms
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NIMP	non investigational medicinal product
NSAID	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OAT	organic anion-transporter
OATP	organic anion-transporting polypeptide
OMIM	Online Mendelian Inheritance in Man
PACL	protocol administrative change letter
PCD	primary completion date
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PDE	phosphodiesterase
PDFF	proton density fat fraction
P-gp	P-glycoprotein
PGx	pharmacogenomic(s)
PI	principal investigator
PK	pharmacokinetic
pmol/L	picomoles per liter
PT	prothrombin time
PVCs	premature ventricular complexes
QD	once daily
QRS	pulses in a heart beat
QT	Q wave to end of T wave
QTc	QT corrected

Abbreviation	Term
QTcF	QTc corrected by Fridericia's formula
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
SoA	schedule of activities
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
T4	thyroxine
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TG	triglycerides
THC	tetrahydrocannabinol
Tmax	time to reach maximum concentration
TRLP	triglyceride-rich lipoprotein particles
TSH	thyroid stimulating hormone
TZD	thiazolidinediones
CCI	[redacted]
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
US	United States
UV	ultraviolet
V	visit
VLDL	very low-density lipoprotein
VCTE	vibration controlled transient elastography
VS	vital signs
Vss	volume of distribution
WBC	white blood cells
WOCBP	women of childbearing potential

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