A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE ORAL DOSES OF PF-06835919 IN HEALTHY ADULT JAPANESE PARTICIPANTS

Study Intervention Number:	PF-06835919
Study Intervention Name:	N/A
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Short Title: A Phase 1 study to evaluate the safety, tolerability, and pharmacokinetics of multiple oral doses of PF-06835919 in healthy adult Japanese participants

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	4 March 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 study to evaluate the safety, tolerability, and pharmacokinetics of multiple oral doses of PF-06835919 in healthy adult Japanese participants

Rationale

KHK is an enzyme catalyzing the conversion of fructose and ATP to F1P and ADP, the first committed step in fructose metabolism. PF-06835919 is a KHK inhibitor that is currently being developed for the treatment of NASH with fibrosis. 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.

In the ongoing 16-week Phase 2a study of PF-06835919 in participants with NAFLD and T2DM (C1061011), 300 mg QD is the highest dose administered. To support Japanese participation in future clinical studies, this study (C1061010) will assess the safety, tolerability and PK of PF-06835919 in healthy adult Japanese participants administered multiple oral doses of 300 mg QD. CCI [redacted]

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of PF-06835919 following multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• Assessment of AEs, clinical laboratory tests, vital signs (including BP and PR) and 12-lead ECG.
• To evaluate the PK of PF-06835919 following single and multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• PK parameters[a] for PF-06835919: Day 1 and Day 7: C_{max}, T_{max}, AUC_{tau} Day 7: $t_{½}$, as data permit.
Exploratory:	**Exploratory:**
• To evaluate the PK parameters of PF-06835919 CCI [redacted] following single and multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• PK parameters[a] for PF-06835919: Day 1 and Day 7: dose normalized C_{max} and AUC_{tau} Day 7: C_{min}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F and V_z/F, as data permit. • CCI [redacted]

a. For complete definition of all PK parameters refer to Section 9.4.1.2.

Overall Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability and PK of multiple oral doses of PF-06835919 300 mg QD in healthy adult Japanese participants.

Number of Participants

A sample size of approximately 8 participants to be assigned to PF-06835919 or placebo in 3:1 ratio (6 active and 2 placebo) has been empirically selected as a compromise between the need to minimize exposure of participants to PF-06835919 and the requirement to provide adequate safety and PK information. No formal statistical inferences will be derived.

Intervention Groups and Duration

Approximately 6 participants are planned to receive 300 mg QD PF-06835919, and approximately 2 participants are planned to receive placebo QD, for 7 days.

Participants will be screened within 28 days of the first dose of study intervention. Eligible participants will be admitted to the CRU on Day -1 and will be required to remain in the CRU until the morning of Day 10 for a total of 10 overnight days. After PK sampling at 72 hours post last dosing, all participants will be discharged from the CRU following completion of the discharge evaluation, which includes adverse event monitoring, physical examination, vital signs, ECG measurements, and safety laboratory tests. Participants will receive a Follow-up telephone contact 28-35 days after the last dose on Day 7. The total duration of participation for each participant, including screening and Follow-up telephone contact, will be approximately 7 to 10 weeks.

Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

Statistical Methods

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, PR, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Plasma concentration of PF-06835919 CCI [redacted] will be descriptively summarized and plotted by nominal PK sampling time and day. The plasma PK parameters for PF-06835919 CCI [redacted] will be summarized descriptively by study day as applicable.

Median trough (predose) plasma concentrations for PF-06835919 CCI will be plotted by day in order to assess the attainment of steady state.

1.2. Schema

Not Applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section 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 Abbreviations used in this table may be found in Appendix 8	**Screening**	**Study Day**											**Follow-up Contact**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -28 to Day -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**28-35 Days[a]**	
Informed Consent	x		Refer to Table 1						Refer to Table 1					
CRU confinement		x		→	→	→	→	→		→	→	x		
CRU discharge												x		
Inclusion/exclusion criteria	x	x												
Medical/medication history (update)	x	x												
Demography, body weight and height	x													
Physical exam[b]	x	x										x		x
Review alcohol and tobacco use	x	x												
Contraception check/review[c]	x	x										x	x	x
Review prior or concomitant treatments	x	x											x	
Single, supine 12-lead ECG	x					x[d]						x		x
Single, supine vital signs (BP and PR)	x					x[d]						x		x
Serious and non-serious adverse event monitoring	x	→		→	→	→	→	→		→	→	x	x	x
PF-06835919 administration[e]				x	x	x	x	x						
Meals/snacks[f]		x		→	→	→	→	→		→	x			
Blood Sampling For:														
Clinical Laboratory tests (after ≥4-hour fast)	x	x				x						x		x

Visit Identifier Abbreviations used in this table may be found in Appendix 8	**Screening**	**Study Day**											**Follow-up Contact**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Day -28 to Day -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**28-35 Days[a]**	
HIV, HBsAg, HBcAb, HBsAb, HCVAb	x													
FSH (for confirmation of postmenopausal status for females only)	x													
Serum pregnancy test (WOCBP only)	x	x										x		x
PF-06835919 [redacted] PK (predose)				x		x		x		x[g]	x[h]	x[h]		x
Urine Sampling For:														
Urine drug testing	x	x												
Urinalysis (and microscopy, if needed)	x	x				x						x		x

a. Contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.
b. Complete physical examination can be performed either at Screening or at Day -1. A brief physical examination at any time point as deemed necessary by the investigator.
c. Contraception check for correct and consistent use (WOCBP only).
d. Predose measurement.
e. Participants will receive PF-06835919/placebo following an overnight fast of at least 8 hours, on Days 1-7 at approximately 0800 hours (±2 hours), approximately 20 minutes prior to the start of breakfast.
f. Breakfast will be provided approximately 20 minutes after morning doses.
g. PK samples collected at 24 and 36 hours (Day 8) following the Day 7 morning dose.
h. PK samples collected at 48 hour (Day 9) and 72 hours (Day 10) following the Day 7 morning dose.

Table 1. List of Procedures for Study Days 1 and 7

Hours Relative to PF-06835919/Placebo Dosing at 0H on Day 1 and Day 7	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**
Inpatient Stay at CRU	→	→	→	→	→	→	→	→	→	→	→
Serious and non-serious adverse event monitoring	→	→	→	→	→	→	→	→	→	→	→
Single, supine 12 lead ECG	x		x								
Single, supine vital signs (BP and PR)	x		x								
PF-06835919/Placebo administration[a]	x										
Meals/snacks[b]	x					x			x		
Blood Sampling For:											
Pfizer Prep D1 Banked Biospecimen(s)[c,d]	x										
Pfizer Prep B2 Banked Biospecimen(s)[c,d]	x										
PF-06835919 [redacted] PK	x	x	x	x	x	x	x	x		x	x
Clinical laboratory tests (after ≥4-hour fast)[e]	x										
Urine Sampling For:											
Urinalysis (and microscopy, as appropriate)[e]	x										

a. Participants will receive PF-06835919/placebo following an overnight fast of at least 8 hours at approximately 0800 hours (±2 hours), approximately 20 minutes prior to the start of breakfast.
b. Breakfast will be provided approximately 20 minutes after morning doses.
c. Pre-dose on Day 1 only. This can be done on Day-1 based on site preference.
d. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
e. Pre-dose on Day 7 only.

2. INTRODUCTION

PF-06835919 is a potent, reversible inhibitor of human KHK that is currently being developed for the treatment of NASH with fibrosis. KHK is an enzyme catalyzing the conversion of fructose and ATP to F1P and ADP, the first committed step in fructose metabolism. Loss of function mutation in KHK, known as Essential Fructosuria, is a rare autosomal genetic condition (Online Mendelian Inheritance in Man or OMIM #229800)[1] which is asymptomatic and only recognized by the appearance of fructose in the urine after fructose consumption.[2,3] 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. In addition, it is anticipated that KHK inhibition will improve circulating lipid and lipoprotein profiles as well as insulin sensitivity.

2.1. Study Rationale

In the ongoing 16-week Phase 2a study of PF-06835919 in participants with NAFLD and T2DM (C1061011), 300 mg QD is the highest dose administered. To support Japanese participation in future clinical studies, this study (C1061010) will assess the safety, tolerability and PK of PF-06835919 in healthy adult Japanese participants administered multiple oral doses of 300 mg QD. CCI [redacted]

2.2. Background

Fructose metabolism, unlike glucose metabolism, is normally not subject to regulatory feedback inhibition in 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 IV bolus of fructose.[4] Depletion of ATP leads to the activation of 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, 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 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 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% and 18% of the US and Japanese populations, respectively, while prevalence of NASH is estimated at 3%-5% of both the US and Japanese population.[15,16] Risk factors for NASH include obesity, insulin resistance, T2DM, hypertension, and dyslipidemia, as manifested by low levels of HDL-C and elevated triglycerides.

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

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

2.2.3. Nonclinical Safety

PF-06835919 was evaluated in safety pharmacology and toxicity studies in Wistar Han rats and beagle dogs up to 6 months and 39 weeks in duration, respectively. Additional studies included genotoxicity assays and female fertility and/or EFD studies in rats and rabbits.

CCI

[redacted]

[redacted]

PF-06835919 displayed no mutagenic or clastogenic potential in any of the genetic toxicology studies conducted. PF-06835919 had an UV light absorbance but was negative in the in vitro phototoxicity assay, indicating it is not phototoxic and no further photosafety testing is recommended.

2.2.4. Clinical Overview

2.2.4.1. Summary of Clinical safety

As of February 2020, there are 4 completed sponsor-initiated clinical trials that administered PF-06835919 (C1061001, C1061002, C1061016, and C1061003). Safety and tolerability findings from these studies are summarized below.

The safety and tolerability of PF-06835919 in healthy adults was assessed in the C1061001 and C1061002 studies, in addition to the C1061016 DDI study. These studies collectively comprised participation of 88 healthy adult males, of which 78 were exposed to at least a single oral dose of PF-06835919, and 62 subjects exposed to repeated doses of PF-06835919. Single oral doses (up to 600 mg) and repeated daily doses (up to 330 mg over 14 days) were found to be well tolerated and generally safe. The DDI segment of C1061002 also demonstrated PF-06835919 was well tolerated and with an acceptable safety profile when co-

administered with atorvastatin. There were no TEAEs of 'severe' intensity across the Phase 1 studies. In C1061001 all TEAEs were 'mild' in intensity. In the C1061002 study, 4 'moderate' intensity TEAEs were reported in active treatment groups: 1 headache with PF-06835919 50 mg; 1 for each of headache and rash with PF-06835919 130 mg; and 1 moderate headache in the DDI segment of the study, reported during PF-06835919 280 mg co-administration with atorvastatin 20 mg. The most frequently reported AE following multiple dose administration of PF-06835919 in Study C1061002 was headache (see IB Section 6.2). In C1061016, the impact of repeated doses (10 days) of PF-06835919 300 mg QD on midazolam PK was evaluated in a 2-way crossover design in 10 healthy participants. The results indicate PF-06835919 was well tolerated when given alone or when co-administered with midazolam, with no new trends in safety laboratory abnormalities, ECG, or vital sign changes of clinical concern. The majority of TEAEs were mild in severity, with 3 episodes of moderate headache experienced by 1 participant (who reported 1 episode following administration of midazolam alone, 1 episode with PF-06835919 alone, and 1 episode following co-administration); 1 participant reporting moderate backpain, and 1 participant reporting hand fracture following co-administration treatment of midazolam and PF-06835919 (sustained through trauma 12 days after discharge from the unit, and determined by investigator to be unrelated to treatment).

In the C1061003 Phase 2 study, PF-06835919 was administered at QD doses of 75 mg, 300 mg, or placebo to a total of 53 participants (of which 26 were female, and 27 male) with NAFLD over a 6-week period. Both dose levels were found to be generally well tolerated with an acceptable safety profile. The majority of TEAEs were mild: 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 due to a moderate TEAE of dysuria.

Cumulatively, 141 adults have participated in sponsor-initiated PF-06835919 clinical trials completed worldwide, with 112 exposed to at least a single oral dose of PF-06835919, and 96 subjects exposed to repeated doses of PF-06835919. In clinical trials to date, there have been no 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, ECGs, or vital signs.

2.2.4.2. Summary of Pharmacokinetic of PF-06835919

Following administration of single oral doses of 10 to 600 mg, PF-06835919 was rapidly absorbed with a median T_{max} ranging from 1 to 3 hours. Following attainment of C_{max}, plasma concentrations declined with a half-life ranging from approximately 11.4 to 15.1 hours. Both the C_{max} and AUC_{24} increased in an approximate dose-proportional manner across the dose range studied.

Following multiple oral doses of PF-06835919 ranging from 15 to 330 mg QD over 14 days, absorption was rapid, with median T_{max} occurring at approximately 0.5 to 1 hour post-dose. Steady-state was achieved within 4 days of dosing. Consistent with study C1061001, AUC_{24} and C_{max} increased in an approximately dose proportional manner over the doses studied. Accumulation of PF-06835919 was modest, with an AUC_{24} accumulation ratio (Day 14/Day 1) averaging from approximately 1.4- to 1.5-fold. No clear dose-related trend in terminal $t_{½}$ was observed, with arithmetic mean values ranging from 13.3 to 16.8 hours. Less than 1% of the oral dose was excreted unchanged in urine.

There was minimal effect of repeated dosing of PF-06835919 on the exposure of a single, oral dose of midazolam in healthy participants (C1061016). The adjusted geometric mean for midazolam AUC_{inf} and C_{max} were similar following co-administration with multiple doses of PF-06835919 as compared to midazolam administration alone. The ratio (90% CI) of the adjusted geometric means of AUC_{inf} and C_{max} for midazolam with multiple doses of PF-06835919, relative to midazolam administered alone were 97.55% (79.91%, 119.08%) and 98.92% (76.44%, 128.01%), respectively.

2.3. Benefit/Risk Assessment

PF-06835919 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

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. CCI

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06835919 may be found in the investigator's brochure, which is the SRSD for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of PF-06835919 following multiple oral doses of PF-06835919 administration in healthy adult Japanese participants. • To evaluate the PK of PF-06835919 following single and multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• Assessment of AEs, clinical laboratory tests, vital signs (including BP and PR) and 12-lead ECG. • PK parameters[a] for PF-06835919: Day 1 and Day 7: C_{max}, T_{max}, AUC_{tau} Day 7: $t_{½}$, as data permit.
Exploratory:	**Exploratory:**
• To evaluate the PK parameters of PF-06835919 and CCI following single and multiple oral doses of PF-06835919 administration in healthy adult Japanese participants.	• PK parameters[a] for PF-06835919: Day 1 and Day 7: dose normalized C_{max} and AUC_{tau} Day 7: C_{min}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F and V_z/F, as data permit. • CCI [redacted]

a. For complete definition of all PK parameters refer to Section 9.4.1.2.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to evaluate the safety, tolerability and PK of multiple oral doses of PF-06835919 300 mg QD in healthy adult Japanese participants.

A total of approximately 8 healthy participants will be enrolled in this study. Participants will be randomized to 2 groups to receive PF-06835919 or placebo treatment with a randomization ratio of 3:1. The overall study design is summarized below in Table 2.

Table 2. Study Design and Treatments

Group	Number of Participants	Treatments[a] (7 Days)
1	6	PF-06835919 300 mg QD
2	2	Placebo QD

a. Study treatment as 3 x 100 mg PF-06835919 or matching Placebo tablets.

All participants will provide informed consent and undergo screening evaluation to determine their eligibility. Participants will be screened within 28 days of the first dose of study intervention. Eligible participants will be admitted to the CRU on Day -1 and will be required to remain in the CRU until morning of Day 10 for a total of 10 overnight days. After PK sampling at 72 hours post last dosing, all participants will be discharged from the CRU following completion of the discharge evaluation, which includes AE monitoring, physical examination, vital signs, ECG measurements, and safety laboratory tests. Participants will receive a Follow-up telephone contact 28-35 days after the last dose on Day 7. The total duration of participation for each participant, including screening and Follow-up telephone contact, will be approximately 7 to 10 weeks.

Participants discontinued prior to completion of the study may, at the discretion of the investigator and sponsor and for reasons other than safety, be replaced by another participant who will repeat the treatment of the participant being replaced.

4.2. Scientific Rationale for Study Design

This study is the first clinical study with PF-06835919 in the Japanese population. The safety and PK of PF-06835919 after multiple dose administration will be collected and evaluated to support inclusion of Japanese participants in future clinical studies of PF-06835919. Placebo treatment is included to maintain the study blind for site and participants to avoid any bias for the safety assessment.

CCI [redacted]

The half-life of PF-06835919 ranged from 11.4 to 16.8 hours, and the plasma concentration seemed to have reached steady state after 4 days of treatment (See Section 2.2.4.2). However, since there is no available information about the disposition of CCI [redacted] in humans, a 7-day treatment is set in this study to secure sufficient dosing duration to attain steady state for both parent (PF-06835919) CCI [redacted]

CCI [redacted] However, all female participants are required to use highly effective methods of contraception during this study (see Appendix 4).

The potential risk of exposure to PF-06835919 in a sexual partner of a male participant in this study via ejaculate is low, and therefore, no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[18]

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

The highest dose in the ongoing PF-06835919 Phase 2a study (C1061011) is 300 mg QD, CCI [redacted] To support Japan's participation in future clinical studies, 300 mg QD is selected in this study to evaluate safety, tolerability and PK of PF-06835919 in healthy adult Japanese participants following multiple oral dose administration.

This dose has been selected based on prior experience in healthy participants and NAFLD patients (see Section 2.2.4.1). PF-06835919 was found to be well-tolerated with an acceptable safety profile with single doses up to 600 mg (C1061001) and repeated doses up to 330 mg/day (C1061002) in healthy participants. A maximum tolerated dose was not identified. In addition, both 75 mg and 300 mg QD dose levels were found to be generally well tolerated with an acceptable safety profile over 6-week treatment in NAFLD patients (C1061003).

CCI [redacted] Based on these in vitro PK characteristics, no meaningful difference would be expected in PF-06835919 PK between Japanese and non-Japanese participants.

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 last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the trial.

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 and female participants must be 18 to 55 years of age, inclusive, at the time of signing the ICD.

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

2. A Japanese participant is defined as having 4 biological Japanese grandparents who were born in Japan.

Type of Participant and Disease Characteristics:

3. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiovascular tests.

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

Weight:

5. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the 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. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

3. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb or HCVAb. Hepatitis B vaccination (positive HBsAb) is allowed.

4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

5. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention (Refer to Section 6.5 for additional details).

Prior/Concurrent Clinical Study Experience:

6. 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 study intervention used in this study (whichever is longer).

Diagnostic Assessments:

7. A positive urine drug test.

8. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest: If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

9. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method (QTcF) and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc 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.

10. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level ≥1.25 × ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusions:

11. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

12. Use of tobacco- or nicotine-containing products in excess of the equivalent >5 cigarettes/day or 2 chews of tobacco per day.

13. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

14. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

15. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any clinical laboratory evaluations, and at least 8 hours prior to the collection of the predose PK sample.

- Water is permitted until 1 hour prior to study intervention administration and may be consumed without restriction beginning 20 minutes after dosing (or beginning of breakfast).

- Participants will not be allowed to eat or drink grapefruit or grapefruit-related-citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention (PF-06835919/placebo) on Day 1 until collection of the final PK blood sample.

- Participants will be dosed following an overnight fast of at least 8 hours.

- **Breakfast** will be served at approximately 20 minutes post-morning dose.

- **Lunch** will be served at approximately 4 hours post-morning dose.

- **Dinner** will be served at approximately 10 hours post-morning dose

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

Participants should be encouraged to consume meals within 25 minutes.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, PR, and ECG measurements), drinking beverages other than water during the first 4 hours after dosing.

5.3.4. 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 or her 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 or partner.

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 study intervention. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-06835919 and matching placebo.

6.1. Study Intervention(s) Administered

6.1.1. Administration

PF-06835919 will be supplied by Pfizer as 100-mg tablets along with matching placebo tablets. Tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Following an overnight fast of at least 8 hours, on Days 1-7 participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours), approximately 20 minutes prior to the start of breakfast. Investigator site personnel will administer study intervention with ambient temperature water to a total volume of approximately 240 mL. Participants may receive additional ambient temperature water up to 100 mL, if needed. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

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.

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 temperatures since previously documented for all site storage locations upon return to business.

3. 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. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site by the sponsor or designee.

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

5. Study interventions should be stored in their original containers.

6. 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), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

7. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's site procedures. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-06835919 tablets and matching placebo tablets will be prepared at the CRU by qualified unblinded site personnel and will be administered in a blinded fashion to the participant.

Study intervention tablets will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced pharmacist. The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.3.2. Breaking the Blind

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be a manual process. 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.

Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. 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. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF/DCT.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.4. Study Intervention Compliance

Study intervention will be administered under the supervision of investigator site personnel. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

In order to minimize any possible effect on PK assessment, females using hormonal contraceptives or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study treatment.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

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

Not Applicable.

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 study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: intolerance of the study drug, SAE, pregnancy, clinically relevant laboratory, vital signs or ECG changes.

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

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 enrolled/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 taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) 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.

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.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention 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 study intervention 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.

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.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether 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.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (PR and BP) should be collected prior to the insertion of the catheter.

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 155 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.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Analysis of efficacy is not applicable to this study.

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 issues.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

8.2.2. Vital Signs

Supine BP will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and PR is acceptable. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) 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 PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTc interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc 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 QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

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

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

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 the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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 study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention or until study completion or withdrawal, whichever is longer.

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

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness 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.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

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, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study 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 study intervention 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

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
- A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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).

Abnormal pregnancy outcomes are considered SAEs. 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 including 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 study intervention.

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.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so 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.

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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. 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 study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength. Exposures to the study intervention 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 study intervention;
- 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 the 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).

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

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

5. Obtain a blood sample for PK analysis at the time specified by the medical monitor if requested by the medical monitor (determined on a case-by-case basis).

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.

8.5. Pharmacokinetics

Blood samples of approximately 3 mL, to provide a minimum of plasma of 1 mL, will be collected for measurement of plasma concentrations of PF-06835919 CCI as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of PF-06835919 CCI Samples collected for analyses of PF-06835919 CCI (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-06835919 CCI [redacted] will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK 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. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in supporting documentation location.

8.8. Biomarkers

8.8.1. Banked Biospecimens for Biomarkers

Additional Banked Biospecimens in this study are:

- 10-mL whole blood (Prep B2 optimized for serum).

Banked Biospecimens will be collected as local regulations and IRB/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. 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. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Sample Size Determination

A sample size of approximately 8 participants to be assigned to PF-06835919 or placebo in 3:1 ratio (6 active and 2 placebo) has been empirically selected as a compromise between the need to minimize exposure of participants to PF-06835919 and the requirement to provide adequate safety and PK information. No formal statistical inferences will be derived.

Participants discontinuing prior to completion of the study for reasons other than safety may, at the discretion of the investigator and sponsor, be replaced by another participant who will repeat all dosings of the participant being replaced.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Evaluable	All participants randomly assigned to and receiving at least 1 dose of study intervention
PK Concentration	The PK concentration population is defined as all participants who receive at least 1 dose of PF-06835919 and who have at least 1 measurable concentration of PF-06835919 [redacted]

Participant Analysis Set	Description
PK Parameter	The PK parameter population is defined as all participants who receive at least 1 dose of PF-06835919 and who have at least 1 of the PK parameters of interest calculated.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe 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 exploratory endpoints.

9.4.1. Primary Endpoint(s)

9.4.1.1. Safety Analyses

All safety analyses will be performed using the safety population.

AEs, ECGs, BP, PR, and safety laboratory data may be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively using sponsor's reporting standards, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

<u>Electrocardiogram Analyses</u>

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

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

Categories for Maximum Post-dose QTcF (msec)				
All participants	≤450	450 - ≤480	480 - ≤500	>500
Categories for Maximum Increase from Baseline in QTcF (msec)				
All participants	≤30	30 - ≤60		>60

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

9.4.1.2. Pharmacokinetic Analyses of PF-06835919

The PK parameters (C_{max}, T_{max}, AUC_{tau} and $t_{½}$) for PF-06835919 following single and multiple dose administration will be derived from the concentration-time profiles as detailed in Table 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.

Table 3. Definition of Plasma PK Parameters for PF-06835919 CCI [redacted]

Parameter	Day(s)	Definition	Method of Determination
AUC_{tau}	1, 7	Area under the plasma concentration time profile from time zero to time tau (τ), the dosing interval, where τ = 24 hours for QD dosing.	Linear/Log trapezoidal method
C_{max}	1, 7	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	1, 7	Time for C_{max}	Observed directly from data as time of first occurrence
C_{min}	7	Minimum plasma concentration during the dosing interval	Observed directly from data
R_{ac}	7	Observed accumulation ratio	Day 7 AUC_{tau}/Day 1 AUC_{tau}
$R_{ac,Cmax}$	7	Observed accumulation ratio for C_{max}	Day 7 C_{max}/Day 1 C_{max}
PTR	7	Peak to trough ratio	C_{max}/C_{min}
$t_{½}$[a]	7	Terminal half life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
CL/F[a,b]	7	Apparent clearance	$Dose/AUC_{tau}$
V_z/F[a,b]	7	Apparent volume of distribution	$Dose/(AUC_{tau} * k_{el})$
AUC_{tau} (dn)[b]	1, 7	Dose normalized AUC_{tau}	AUC_{tau}/Dose
C_{max}(dn)[b]	1, 7	Dose normalized C_{max}	C_{max}/Dose
CCI [redacted]	[redacted]	[redacted]	[redacted]

a. As data permit.
b. To be calculated for PF-06835919 only.
C [redacted]

The plasma PK parameters for PF-06835919 will be summarized descriptively by study day as applicable.

9.4.2. Exploratory Endpoint(s)

The PK parameters for PF-06835919 (additional parameters other than those in Section 9.4.1.2) and CCI following single and multiple dose administration of PF-06835919 will be derived from the concentration-time profiles as data permit. The PK parameters to be assessed are shown in Table 3.

Plasma concentration of PF-06835919 and CCI will be descriptively summarized and plotted by nominal PK sampling time and day. The plasma PK parameters for PF-06835919 and CCI will be summarized descriptively by study day as applicable. Median trough (predose) plasma concentrations for PF-06835919 and CCI will be plotted by day in order to assess the attainment of steady state.

CCI

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, and/or supporting clinical development.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), 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 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 study intervention, 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. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, 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.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional 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 specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.3. 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 will 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 participants 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 and medical record identification. 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.

10.1.4. 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 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 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 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. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

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 corresponding study results are 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 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 contributes 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.

10.1.5. 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 IQMP.

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.

10.1.6. 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 eCRF that are 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 investigator site file.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

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 sponsor or designee/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.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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.

10.1.8. 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 the 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.

10.1.9. 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 CTMS.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention 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. For sites other than a Pfizer CRU, 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 safety 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 issues.

Table 4. Protocol-Required Safety Laboratory Assessments

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/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• Urine drug screening[c] • Pregnancy test (β-hCG)[d] <u>At screening only:</u> • FSH[b] • Hepatitis B surface antigen • Hepatitis B core Antibody • Hepatitis B surface antibody • Hepatitis C antibody • Human immunodeficiency virus

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; qual = qualitative; RBC = red blood cell; WBC = white blood cell.

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Serum β-hCG for female participants of childbearing potential.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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 <u>Meeting</u> 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. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• 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 CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention 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 study intervention under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and 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 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 study intervention caused the event, then the event will be handled as "related to study intervention" 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 providers.

- 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

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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 no menses for 12 months without an alternative medical cause. In addition, a

     - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.

     - For women using HRT, FSH should be measured after an appropriate washout of HRT (at least 14 days after the last dose of HRT). HRT must be discontinued at least 28 days before the first dose of investigational product and for at least 28 days after the last dose of PF-06835919.

     - Females whose menopausal status is in doubt will be required to use one of the allowed non-hormonal highly effective contraception methods.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Non-hormonal Intrauterine device (IUD).

2. Bilateral tubal occlusion.

3. Vasectomized partner.

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP 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.

10.5. Appendix 5 Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-06835919 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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 DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede 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, CK, direct and indirect bilirubin, GGT, PT/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/paracetamol (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 samples for acetaminophen/paracetamol 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 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 <u>May</u> Qualify as Adverse Events

- 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 PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as Serious Adverse Events

- 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 participants 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 participants 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 (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >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: Abbreviation

The following is a list of abbreviations that used in the protocol.

Abbreviation	Term
Abs	absolute
ADP	adenosine diphosphate
AE	adverse event
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time curve from zero to infinity
AUC_{24}	area under the plasma concentration-time curve from zero to 24 hours
AUC_{tau}	area under the plasma concentration-time curve over dosing interval
AV	atrioventricular
BCRP	breast cancer resistance protein
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent clearance
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CTMS	clinical trial management system
CYP	cytochrome P450
DCT	data collection tool
DDI	drug drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
dn	dose normalized
DNA	deoxyribonucleic acid

Abbreviation	Term
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	embryo fetal development
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F1P	fructose-1-phosphate
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL-C	high density lipoprotein – cholesterol
hERG	human ether-a-go-go related gene
Hg	mercury
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
IC_{50}	50% inhibition of concentration
ICD	informed consent document
ICH	International Council for Harmonisation
IND	investigational new drug application
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IQMP	Integrated Quality Management Plan
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
k_{el}	terminal phase rate constant
KHK	ketohexokinase
LBBB	left bundle branch block
LFT	liver function test
Log	logarithm

Abbreviation	Term
LV +dP/dt max	maximum rate of rise in left ventricular pressure (index of myocardial contractility)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
CCI [redacted]	[redacted]
msec	millisecond
MW	molecular weight
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
Nav	nerve artery vein
NOAEL	no-observed-adverse-effect level
NOEL	no observed effect level
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
P-gp	P-glycoprotein
PCRU	Pfizer clinical research unit
PDE	phosphodiesterase
PK	pharmacokinetic
PR	pulse rate
PT	prothrombin time
PTR	peak to trough ratio
PVC	premature ventricular contraction/complex
QD	once daily
QT	measure between Q wave and T wave
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
R_{ac}	observed accumulation ratio
$R_{ac, Cmax}$	observed accumulation ratio for C_{max}
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedures
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment emergent adverse event

Abbreviation	Term
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
$t_{½}$	terminal half-life
T2DM	type 2 diabetes mellitus
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
US	United States
UV	ultraviolet
VLDL	very low density lipoprotein
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	women of child-bearing potential

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