A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, PARALLEL-COHORT STUDY TO COMPARE THE PHARMACOKINETICS OF PF-06865571 IN ADULT PARTICIPANTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT HEPATIC IMPAIRMENT

Investigational Product Number:	PF-06865571
Investigational Product Name:	Not Applicable
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	C2541009
Phase:	1

Short Title: A STUDY TO INVESTIGATE THE EFFECTS OF HEPATIC IMPAIRMENT ON THE PHARMACOKINETICS OF PF-06865571

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	27 June 2019	Not applicable (N/A)

TABLE OF CONTENTS

LIST OF TABLES

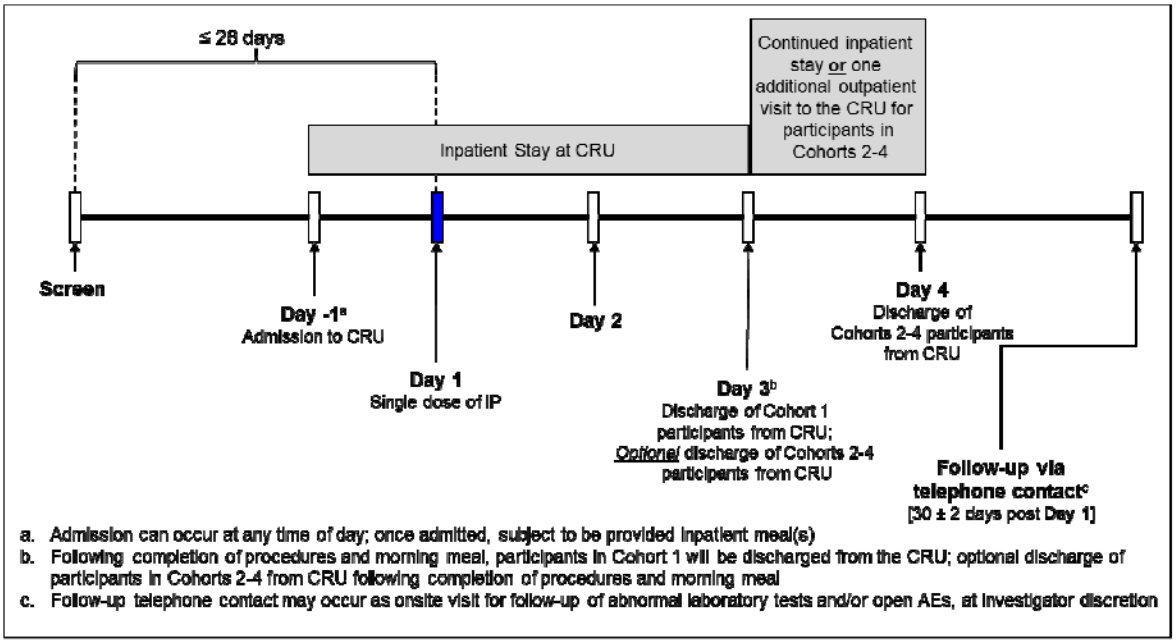
LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Not applicable.

1.2. Schema



1.3. Schedule of Activities (SoA)

The table provides an overview of the protocol visits and procedures. Refer to 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/Day *[for list of abbreviations refer to Section 10.9]*	**Screen** ≤-28 to -2	**Day** -1	**Day 1**												**Day 2**		**Day** 3[a]	**Day** 4[a]	**ET**	**Follow-Up**
Hours Post Dose		--	0	0.5	1	2	4	6	7	8	10	12	14	16	24	36	48	72	--	--
Informed consent & demography	x																			
Outpatient visit	x																	x[a]	x	
Inpatient stay at Clinical Research Unit		x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x[a]	x[a]		
Eligibility assessment	x	x																		
Medical history	x	x																		
Physical exam (height & body weight at Screen, only)[b]	x	x															x[c]	x[c]	x	
Breath alcohol test	x	x																		
Alcohol/tobacco & contraception use	x	x																x[c,d]	x	x[e]
(Update) prior/concomitant treatments	x	x																x[c,d]	x	x
Single, *supine* 12-lead ECG	x		x														x[c]	x[c]	x	
Single, *seated* vital sign assessment (BP and pulse rate)	x		x														x[c]	x[c]	x	
Serious and non-serious adverse event monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x[c]	x[c]	x	x
Standard meals[f]		x	x				x		x		x		x		x		x	x[c]		
Investigational product administration			x[g]																	
Blood for clinical laboratory tests after ≥4-hour fast	x		x														x[c]	x[c]	x	
Blood FSH (females only), HIV, HBsAg, HCVAb/RNA	x																			
Blood for pregnancy test (females only)	x		x														x[c]	x[c]	x	
CCI																				
Blood for pharmacokinetic sampling for PF-06865571			x	x	x	x	x	x		x	x	x		x	x	x	x	x[c]	x	
Urine drug test		x																		
Urinalysis (and microscopy, if needed)	x		x														x[c]	x[c]	x	
Urine pregnancy test (WOCBP, only)			x																	

a. Participants discharged post completion of procedures (Cohort 1, *only*); in Cohorts 2-4, discharge (with subsequent outpatient visit) permitted *or* stay can continue to Day 4.
b. Full physical (PE) exam at Screen; at all other time points, limited PE for findings during previous PE or new/open AEs *only*, at Investigator discretion.
c. **On Day 3**, procedures limited to Cohort 1, *only*; **on Day 4**, procedures limited to Cohorts 2-4, *only*.
d. In Cohorts 2-4 *only*, procedures to be completed *only if* participant is discharged on Day 3 and returns for outpatient visit on Day 4.
e. Confirmation of appropriate contraception use *only*.
f. Meals/snacks to be served at clock times matching approximately 0H, 4H, 7H, 10H, and 14H (optional) relative to dosing on Day 1 (while inpatient).
g. Dosing to occur with standard morning meal provided approximately 30 minutes prior to 0H, and completed approximately 10 minutes prior to dosing.

2. INTRODUCTION

Diacylglycerol acyltransferases (DGATs) catalyze the terminal step in triglyceride (TG) synthesis; specifically, the esterification of a fatty acid (FA) with diacylglycerol (DAG) resulting in the formation of TG.[1] In mammals, 2 structurally unrelated DGAT enzymes (DGAT1 and DGAT2) have been characterized. DGAT1 is highly expressed in the intestine and plays a central role in fat absorption.[2] DGAT2 is highly expressed in liver and adipose.[3] PF-06865571 is an oral, small molecule DGAT2 inhibitor that is postulated to decrease hepatic TG synthesis and hepatic lipid burden in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Based on observations in nonclinical studies conducted with PF-06865571, it is hypothesized that DGAT2 inhibition will impact both physiological drivers contributing to NASH via direct inhibition of liver triglyceride synthesis, as well as adaptive responses leading to reduction in hepatic de novo lipogenesis (DNL). Following 2 weeks of dosing in participants with NAFLD, PF-06865571 has been shown to reduce liver fat in a dose-responsive manner.

2.1. Study Rationale

The primary purpose of this non-randomized, open-label study is to characterize the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics (PK) of PF-06865571 following administration of a single, oral, 100 mg dose of PF-06865571. NAFLD/NASH is associated with varying degrees of hepatic impairment. Recognizing that the target population of PF-06865571 is patients with NAFLD/NASH and CCI [redacted] the current study is proposed to evaluate whether there is any clinically meaningful effect of hepatic impairment on the plasma PK of PF-06865571.

2.2. Background

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

2.2.3. Clinical Overview

As of the issuance of this protocol, 6 clinical studies have completed dosing with PF-06865571 (C2541001, C2541002, C2541003, C2541005, C2541006, and C3711002). Refer to the PF-06865571 investigator's brochure for more details on Studies C2541001, C2541002, C2541003, and C3711002. CCI [redacted] A total of 168 participants have been randomized across the 6 clinical studies and exposed to at least 1 dose of the investigational product (PF-06865571, and/or matching placebo) across the clinical studies conducted with PF-06865571.

CCI [redacted]

[redacted]

2.3. Benefit/Risk Assessment

PF-06865571 is not expected to provide any clinical benefit to participants in this study. This study is designed primarily to generate pharmacokinetic data to inform further clinical development in the target population of patients with NASH. The data from this study will contribute to dosing recommendations of PF-06865571 for the treatment of NASH acknowledging that the target patient population includes those with varying degrees of hepatic impairment.

PF-06865571 has been administered as single doses in healthy subjects, as repeated doses in healthy adults and patients with NAFLD, and as modified-release formulation, as well as in combination with metformin. It has been observed to be well-tolerated with an acceptable safety profile at single oral doses as high as 1500 mg and repeated, oral doses of up to 1800 mg/day (as 600 mg every 8 hours [Q8H]) for a duration of up to 14 days with the maximum tolerated dose not identified. As of the issuance of this protocol, no specific human risks have been identified. The clinical impact of any *potential* risks in this study will be minimized through the proposed close, inpatient monitoring during the dosing period along with the selection of a dose (100 mg) which is 15-fold lower than the highest single dose administered thus far.

Based on the safety profile of PF-06865571 observed in clinical studies to date, the risk to the participants in this study is deemed to be minimal. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06865571 may be found in the investigator's brochure for PF-06865571, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of PF-06865571 following administration of a single oral dose in adult participants with varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.	• PF-06865571 PK parameters derived from plasma: C_{max}, AUC_{last}, and AUC_{inf}.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of a single oral dose of PF-06865571 when administered to adult participants with varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.	• Assessment of treatment-emergent adverse events, clinical laboratory tests, vital signs, and 12-lead ECGs.
CCI [redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, non-randomized, open-label, single-dose, parallel-cohort, multicenter study to compare the pharmacokinetics of PF-06865571 in adult participants with varying degrees of hepatic impairment relative to participants without hepatic impairment after a single, oral 100 mg dose administered in the fed state. A total of approximately 24 participants with varying degrees of hepatic function will be dosed in the study as shown in Table 1.

Table 1. Hepatic Function Categories Based on Child Pugh Score

Cohort	Description	Child-Pugh Score	Number of Subjects
1	Without hepatic impairment	Not Applicable	6a
2	Mild hepatic impairment	Class A (5 to 6 points)	6
3	Moderate hepatic impairment	Class B (7 to 9 points)	6
4	Severe hepatic impairment	Class C (10 to 15 points)	6b

a. Additional participants may be dosed to a maximum of 8 participants to ensure mean age ±5 years and mean body weight ±10 kg of this cohort is aligned with the pooled average assessed when ≥75% of participants are dosed across the other 3 cohorts.

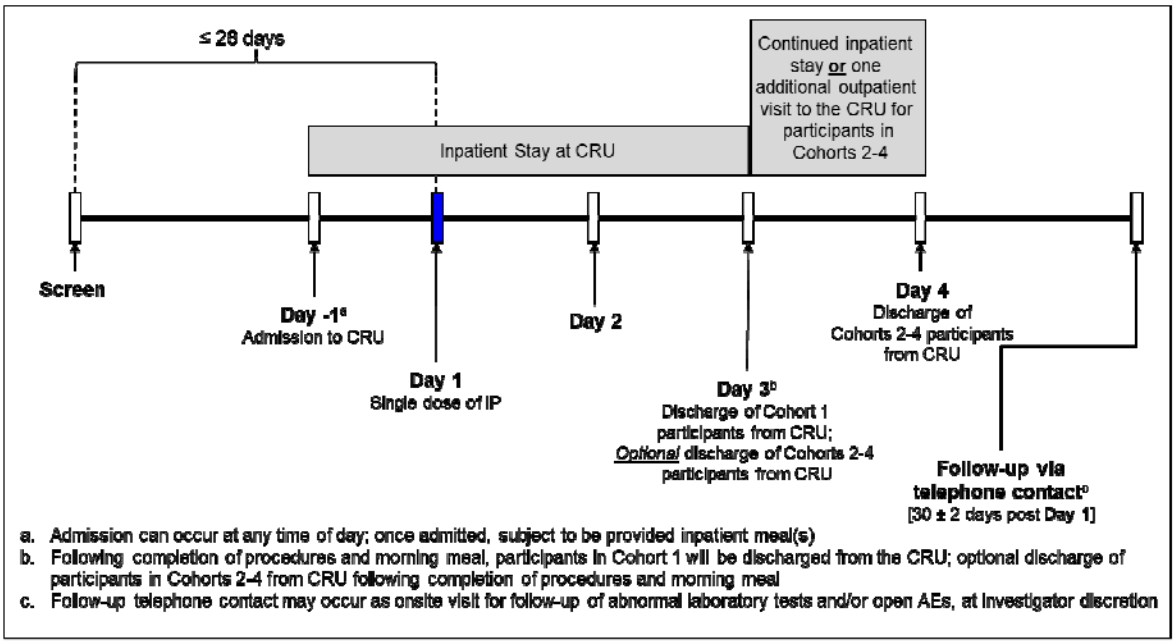
b. If recruitment across the sites selected proves to be prohibitive, study will dose only 4 participants in this cohort.

Categorization of participants into Cohort 2-4, inclusive, will be done based on Child-Pugh scores determined, as described in Appendix 8, at the Screening visit. Participants will be dosed in a staged manner such that those with moderate and severe hepatic impairment (Cohorts 3 and 4) will be evaluated first. Dosing in participants with mild hepatic impairment (Cohort 2) will initiate when approximately 50% of the total participants in Cohorts 3 and 4 have been dosed. Participants without hepatic impairment (Cohort 1) will be recruited near the end of the study to match the average demographics (at a minimum, age and weight; and gender as much as practically possible) across the pooled Cohorts 2 through 4. **Approval from the sponsor must be obtained before proceeding with recruitment for participants in Cohort 1 or Cohort 2.**

Participants who prematurely discontinue for non-safety related reasons may be replaced, at the discretion of the principal investigator (PI) and sponsor study team.

The overall study design is summarized in Figure 1. For individual participants, the total duration of participation from the Screening visit to the follow-up visit will range from 5 weeks (minimum) to 9 weeks (maximum).

Figure 1. Study Design



4.2. Scientific Rationale for Study Design

This study involves participants with varying degrees of hepatic impairment and participants without hepatic impairment, matched for age as well as body weight (and gender as much as practically possible). A single dose of PF-06865571 is proposed since single dose plasma PK is generally predictive of exposure upon repeated dosing, especially given that the observed relatively short terminal half-life ($t_{½}$) of PF-06865571 resulted in minimal accumulation upon repeated dosing of both Q8H and Q12H frequency.

CCI [redacted] serial PK samples will be collected over 48 hours in participants without hepatic impairment (Cohort 1). [redacted] serial PK samples will be collected over 72 hours postdose to adequately characterize the elimination phase of the plasma concentration-time profile in the cohorts with varying degrees of hepatic function (Cohorts 2-4).

Malnutrition is prevalent in patients with chronic liver disease, and regular meals are an important aspect for their health. CCI [redacted] PF-06865571 administration is planned to occur with the morning standard meal in this study to ensure consistency with the intended dosing scheme in the target patient population.

In general, participants with normal hepatic function (Cohort 1) will abstain from all concomitant treatments, except for the treatment of adverse events. Participants with impaired hepatic function (Cohorts 2, 3, and 4) are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s) with some exclusions. Specfically, strong CYP3A inhibitors, strong and moderate CYP3A inducers, and time-dependent inhibitors of CYP3A are excluded from this study in participants with impaired hepatic function [redacted]. In addition, moderate CYP3A inhibitors will not be co-administered with PF-06865571 on Day 1 of this study. Similarly, BCRP substrates (eg, rosuvastatin) and sensitive CYP2C9 substrates will not be administered on Day 1 [redacted]. P-gp inhibitors (eg, digoxin) are excluded from this study. [redacted] articipants taking metformin must not take a morning dose of metformin on Day 1 of this study.

The Child-Pugh classification (CPC; refer to Appendix 8) will be used to define the 3 cohorts of participants with varying degrees of hepatic impairment. This study will include participants with mild (Child-Pugh Class A, Cohort 2), moderate (Child-Pugh Class B, Cohort 3), and severe (Child-Pugh Class C, Cohort 4) hepatic impairment as well as demographic-matched control participants without hepatic impairment (Cohort 1). All 3 categories of hepatic impairment will be assessed, as these represent the likely population in later phase studies for the proposed indication of treatment of NASH. All participants will be required to provide their own consent to participate in this study, hence participants with clinically-active Grade 3 or Grade 4 encephalopathy will be excluded. However, participants who have a ***previous*** history of Grade 3 or Grade 4 encephalopathy but are currently receiving an intervention [for example: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to control their encephalopathy-related signs and symptoms are eligible provided the ***on-treatment*** encephalopathy grading at the Screening visit is Grade 2 or lower thereby permitting them to provide their own informed consent. Acknowledging the medical state of the population enrolled, certain eligibility criteria for participants with hepatic impairment are distinctly different, including assessment of Hepatitis B and Hepatitis C, with no specific exclusion of those who have these conditions planned for participants classified in Cohorts 2, 3, or 4.

[redacted] participants will be excluded if there is concomitant clinical evidence of renal impairment, defined as estimated glomerular filtration rate (eGFR) ≤60 mL/min. This is to enable a more clear assessment of the effect of hepatic impairment on PF-06865571 disposition.

CCI [redacted] all female participants of childbearing potential, at risk of pregnancy, are required to use highly effective methods of contraception during this study. In addition, male participants must use barrier methods of contraception to minimize transfer of drug to their female partner(s). Refer to Section 10.4 for details regarding contraception guidance.

CCI [redacted]

4.3. Justification for Dose

A single oral dose of 100 mg PF-06865571 will be used in this study. Dosing will occur in the fed state, consistent with previous clinical studies with PF-06865571. This dose has been selected based on prior experience in healthy participants and also takes into considerations that participants with varying degrees of hepatic impairment may have an increase in plasma PF-06865571 exposure. PF-06865571 was found to be well-tolerated with single doses up to 1500 mg (C2541001) and repeated doses up to 1800 mg/day (600 mg Q8H; C2541002) with the maximum tolerated dose not identified when administered to healthy adult participants. The PK of PF-06865571 is approximately dose-proportional, and the results at the proposed dose of 100 mg in this study can be extrapolated to other doses. While the PF-06865571 dose in this study represents half the maximum total daily dose/exposure of 300 mg BID envisioned in the Phase 2b, dose-ranging/dose-finding study, it is likely to be within the efficacious dose range (based on effect on liver fat observed following 14-days of dosing in those with NAFLD in Study C2541005).

For a single 100 mg dose of PF-06865571, Simcyp® simulations predict C_{max} increases of 1.2-, 1.3-, and 1.5-fold in participants with Child-Pugh classifications A, B, and C, respectively. AUC_{inf} increases of 1.4-, 2.1-, and 2.9-fold, respectively, are also predicted. The terminal $t_{½}$ is predicted to increase by <2-fold. In addition, these predictions are in line with less than 3-fold exposure increases observed in participants with moderate or severe hepatic impairment in clinical studies with sensitive CYP3A substrates, including midazolam and triazolam.[4,5] Thus, a 3-fold increase likely represents the worst-case estimate for change in plasma exposure in this study in those with severe hepatic impairment and are not likely to pose a safety concern if observed in this study.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the follow-up visit via telephone contact shown in the schedule of activities.

The end of the study is defined as the date of the follow-up visit via telephone contact, shown in the schedule of activities, for the last participant in the trial globally.

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

5.1.1. Participants in All Cohorts

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 between the ages of 18 (or the minimum country-specific age of consent if >18) and 70 years, inclusive, at the Screening visit:

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

Type of Participant and Disease Characteristics:

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

Weight:

3. Body mass index (BMI) of 17.5 to 35.4 kg/m^2, inclusive; and a total body weight >50 kg (110 lb), at the Screening visit; with a single repeat assessment of total body weight (and hence BMI), *on a separate day* permitted to assess eligibility, if needed.

Informed Consent:

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

5.1.2. *Additional* Inclusion Criteria for Participants without Hepatic Impairment (Cohort 1 *Only*)

1. At Screening, no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG and clinical laboratory tests, as assessed by the sponsor-identified central laboratory.

2. At Screening, participants must meet the demographic-matching criteria, including:

   - A body weight that is ±10 kg of the average of the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4), as provided by the sponsor;

   - An age that is ±5 years of the average of the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4), as provided by the sponsor;

   - ***Attempts will be made*** to ensure that the male-to-female distribution in Cohort 1 is comparable to that in the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4).

3. No known or suspected hepatic impairment; including at Screening. Partcipants meet **all** the following criteria, as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed:

   - Alanine aminotransferase (ALT) ≤ upper limit of normal (ULN);

   - Aspartate aminotransferase (AST) ≤ ULN;

   - Total bilirubin ≤ ULN;

     NOTE: Participants with a history of Gilbert syndrome (and hence elevated total bilirubin) are eligible provided direct bilirubin level is ≤ ULN **plus** ALT and AST are ≤ ULN **plus** alkaline phosphatase, hemoglobin, and reticulocyte count are all ≤ ULN;

   - Albumin ≤ ULN;

   - Prothrombin time ≤ ULN.

5.1.3. *Additional* Inclusion Criteria for Participants with Impaired Hepatic Function (Cohorts 2, 3, and 4 *Only*)

1. Stable hepatic impairment that meets the criteria for Class A, B, ***or*** C of the modified Child-Pugh classification (refer to Appendix 8) with no clinically significant change in disease status within the 28 days prior to the Screening visit, as documented by the participant's recent medical history (*for example*: no worsening clinical signs of hepatic impairment, no worsening of total bilirubin or prothrombin time (PT) by more than 50%).

2. Stable concomitant medications for the management of individual participants' medical history; ***on a case-by-case basis***, with input from the sponsor, participants receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control.

3. Participant is willing and able to abide by the lifestyle guidelines described in Section 5.4 of this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, ileal resection).

   NOTE: Participants who have undergone cholecystectomy and/or appendectomy are eligible for this study as long as the surgery occurred more than 6 months prior to Screening.

2. At Screening, participants with a positive result for human immunodeficiency virus (HIV) antibodies, as assessed by sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed.

3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

4. Use of prior/concomitant therapies as outlined in Section 6.5.

Prior/Concurrent Clinical Study Experience:

5. 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 investigational product used in this study (whichever is longer).

6. Participants with known prior participation (ie, randomized and received at least 1 dose of investigational product) in a study involving PF-06865571.

Diagnostic Assessments:

7. A positive urine drug test, for illicit drugs on Day -1, as assessed by sponsor-identified central laboratory. However, ***participants in Cohorts 2-4, only***, who have been medically prescribed opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at the screening visit will be allowed to participate.

   NOTE: repeat urine drug testing is not permitted in this study.

8. At Screening ***or*** Day -1, a positive breath alcohol test, as assessed using kits provided by sponsor-identified central laboratory, with a single repeat *on a separate day* permitted to assess eligibility, if needed.

Other Exclusions:

9. Male participants with partners who are currently pregnant.

10. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing and until the follow-up contact.

11. History of sensitivity to heparin or heparin-induced thrombocytopenia, only if heparin is used to flush intravenous catheters used during serial blood collections.

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

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

5.2.1. *Additional* Exclusion Criteria for Participants without Hepatic Impairment (Cohort 1 *Only*)

Participants presenting with any of the following will not be included in the study:

1. Evidence of chronic liver disease including history of hepatitis, hepatitis B, or hepatitis C or evidence of any of the following, as assessed by sponsor-identified central laboratory, with a single repeat, permitted to assess eligibility, if needed:

   - Hepatitis B virus, defined by presence of hepatitis B surface antigen (HBsAg);

     NOTE: while *not* part of the tests assessed in this study, participants with a previously positive hepatitis B surface antibody result due to vaccination are deemed eligible;

- Hepatitis C infection, defined by presence of hepatitis C antibody (HCVAb) ***and*** HCV ribonucleic acid (RNA).

2. 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).

3. Screening ***supine*** 12-lead ECG demonstrating Fridericia method-corrected QT (QTcF) interval >450 millisecond (msec) or a QRS interval >120 msec. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility.

4. Screening ***seated*** systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg, following ≥5 minutes of seated rest. If SBP is ≥140 mm Hg or DBP ≥90 mm Hg, the blood pressure (BP) assessment should be repeated 2 more times and the average of the 3 BP values should be used to determine eligibility.

5. Use of ***chronic*** prescription medications within 7 days or 5 half-lives (whichever is longer) prior to Day 1;

   NOTE: Use of selected, limited prescription and non-prescription medications is permitted (refer to Section 6.5 for details).

6. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

5.2.2. *Additional* Exclusion Criteria for Participants with Impaired Hepatic Function (Cohorts 2, 3, and 4 *Only*)

Participants presenting with any of the following will ***not*** be included in the study:

1. Hepatic carcinoma ***or*** hepatorenal syndrome ***or*** limited predicted life expectancy (defined as less than 1 year in Cohorts 2 & 3 and less than 6 months for Cohort 4 only).

2. A diagnosis of hepatic dysfunction secondary to any acute ongoing hepatocellular process that is documented by medical history, physical examination, liver biopsy, hepatic ultrasound, computerized tomography scan, or magnetic resonance imaging (MRI).

3. History of surgery that would be expected to alter absorption, distribution, metabolism, or excretion (ADME) properties of PF-06865571 (eg, status post porta-caval shunt surgery);

   NOTE: Participants with a transjugular intrahepatic portosystemic shunt (TIPS) are permitted provided that they meet the Child-Pugh criteria.

4. History of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than **4 weeks** prior to Screening.

5. Signs of clinically active Grade 3 or Grade 4 hepatic encephalopathy (ie, > Grade 2 Portal Systemic Encephalopathy score; refer to Appendix 8).

6. Severe ascites and/or pleural effusion, except for those categorized in Cohort 4 who may be enrolled provided participant is medically stable, per the investigators' medical judgment.

7. Participants who have previously had a transplanted kidney, liver, or heart.

8. Screening ***supine*** 12-lead ECG demonstrating a QTcF interval >480 msec or a QRS interval >120 msec. If QTcF exceeds 480 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine eligibility.

9. At Screening, persistent severe, uncontrolled hypertension; for example: ***seated*** systolic blood pressure (SBP) ≥180 mm Hg and/or diastolic blood pressure (DBP) ≥105 mm Hg after ≥5-minute of seated rest, with a single repeat permitted to assess eligibility, if needed, at each of these 2 visits:

   - For participants with SBP ≥160 (and <179) mm Hg ***or*** DBP ≥100 (and <104) mm Hg, the period between Screening and Day -1 must be used to refine the doses of the agents used for management of blood pressure with the aim to have stable BP by Day 1 [refer to Section 5.3].

10. Participants with ALT ***or*** AST >5x ULN on clinical laboratory tests at Screening, as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed.

11. At Screening, participants with an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation, and serum creatinine (SCr), as assessed by the sponsor identified central laboratory, with a single repeat permitted to assess eligibility, if needed.

5.3. Criteria for Dosing on Day 1

Participants will progress to dosing on Day 1 provided they have satisfied all the following criteria:

- Breath alcohol test, using kits provided by sponsor-identified central laboratory, on Day -1 is negative;
- In females of childbearing potential, urine pregnancy test on Day 1 is negative as reported by on-site pregnancy test using supplies provided by the sponsor-identified central laboratory;
- Safety-related laboratory tests collected and analyzed by sites' local laboratory on Day -1, ***if performed*** at investigator discretion, upon review on Day 1 must reflect the participant to be in stable medical condition;
- Cohort 1 only: Approval from the sponsor must be obtained before proceeding with dosing participants in Cohort 1;
- Cohorts 2 and 3 only: Participants must have measurement on Day 1 of SBP ≤159 mm Hg ***and*** DBP ≤99 mm Hg –
  - A single repeat assessment is permitted, to confirm that the above criterion is met [and in such cases, the repeat assessment overrides initial results];
- Cohort 4 only: Participants must have measurement on Day 1 of SBP ≤159 mm Hg ***and*** DBP ≤105 mm Hg –
  - A single repeat assessment is permitted, to confirm that the above criterion is met [and in such cases, the repeat assessment overrides initial results].

5.4. Lifestyle Considerations

After confirmation of eligibility, the participants will be instructed to maintain the guidelines described below for the duration of participation in the study.

5.4.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to all fasting clinical laboratory evaluations and at least 10 hours prior to the collection of the predose pharmacokinetic (PK) sample;
- Water may be consumed as desired (ad libitum);

- While inpatient, all meals will be standardized as follows:

  - On Day 1, following an overnight fast of at least 10 hours, participants should begin breakfast approximately 30 minutes prior to PF-06865571 administration. The breakfast will be consumed over approximately a 20-minute period with PF-06865571 administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to complete the entire breakfast. There will be no water restrictions prior to dosing.

  - Standard morning meal, lunch, afternoon snack, and evening meal (and an optional evening snack) will be provided at a similar clock time to the clock time when these meals are provided relative to dosing on Day 1 (ie, 0H, 4H, 7H, 10H, and 14H);

  - The total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The nutritional macronutrient composition consumed by each participant should be maintained, as much as practically possible;

  - The daily caloric intake per participant should not exceed approximately 3200 kcal;

  - The morning meal (matching 0H), afternoon snack, and optional evening snack is each envisioned to constitute 300 to 400 calories and a macronutrient composition of approximately 55% carbohydrates, 30% fat and 15% protein;

  - Lunch and evening meal ***each*** is envisioned to constitute less than 1000 calories;

  - Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to Day 1 and until collection of the final PK blood sample.

5.4.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from alcohol for ≥24 hours prior to admission for inpatient stay (plus have a negative breath alcohol test on Day -1) and continue abstaining from alcohol until the follow-up contact;

- Consumption of caffeinated drinks and nicotine containing products is permitted during participation in the study; however, there may be a need for brief interruption while at the site, depending on local site policy.

5.4.3. Activity

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

5.4.4. Contraception

At the Screening visit, 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 schedule of activities (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.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently dosed on Day 1. Screen failure data are collected and remain as source with only a limited set reported in the clinical database.

In ***this study,*** participants may be re-screened. This is permitted when, due to ***logistical constraints***, the maximum period between Screening Visit and Day 1, of **28 days,** is exceeded. In addition, for participants in Cohorts 2-4, inclusive, ***only***, re-screening may be appropriate following mild intercurrent illness after the condition has resolved. In such cases, all screening procedures must be repeated and the participant assigned a new 8-digit study-specific identification (SSID) number. Participants must be deemed to meet all the eligibility criteria under the new 8-digit SSID *before* progressing to Day 1.

6. STUDY INTERVENTION

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

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

6.1. Study Intervention(s) Administered

For this study, the investigational product is PF-06865571, supplied by Pfizer as tablets, each containing 100 mg of active drug.

Tablets will be supplied to the clinical research unit (CRU) as packaged bottles for unit dosing and labeled according to local regulatory requirements.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive breakfast as outlined in Section 5.4.1 (Meals and Dietary Restrictions). The participants will then receive investigational product at approximately 08:00 hours (plus or minus 2 hours). Investigator site personnel will administer investigational product with ambient temperature water to a total volume of ***approximately 120 mL***. Participants will swallow the investigational product whole, and will not manipulate or chew the investigational product 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, as applicable for temperature-monitored shipments.

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

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product (IP) manual.

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

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

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

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

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of investigational product, 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.

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

PF-06865571 will be prepared by qualified site personnel according to the IP manual.

The PF-06865571 tablet will be provided to the participant in a unit dose container.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Following completion of informed consent at the Screening visit, each participant will be assigned a single 8-digit SSID number by the site staff. The first 4 digits of the SSID will reflect the sponsor-assigned site number and the remaining 4 digits will reflect each participant's unique number assigned in chronological order of when informed consent is obtained. ***Separately***, prior to dosing on Day 1, each participant will be assigned a 4-digit number consisting of site number (first digit), cohort (second digit) and chronological order of dosing, at a given site (third and fourth digit).

6.4. Study Intervention Compliance

Investigational product will be administered under the supervision of investigator site personnel. The oral cavity of each participant will be examined following dosing to ensure the investigational product was swallowed.

6.5. Concomitant Therapy

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.

Treatments taken ***within 28 days*** before dosing on Day 1 will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments.

Females using hormonal contraceptives or taking hormone replacement therapy are eligible to participate in this study.

6.5.1. Participants Without Hepatic Impairment (Cohort 1, Only)

In general, participants will abstain from all concomitant treatments, except for the treatment of adverse events. Of note, the following ***restrictions:***

- Acetaminophen/paracetamol may be used at doses of ≤1 g/day;
- Herbal supplements must be discontinued ***at least 28 days prior*** to Day 1 and until the follow-up contact;
- Limited use of prescription and non prescription medications that are not believed to affect the overall results of the study may be permitted on a case by case basis ***after*** approval by the sponsor study team.

6.5.2. Participants with Impaired Hepatic Function (Cohorts 2, 3, and 4)

Participants are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s). ***Whenever possible***, attempts must be made to ***not*** alter the doses and regimens of the concomitant medications after Day 1 and until the follow-up contact.

- Participants on the following medications, at the Screening visit, are ***excluded*** from the study:
  - Potent CYP3A inhibitors (eg, boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole);
  - Time-dependent CYP3A inhibitors (eg, diltiazem, erythromycin, and verapamil);

- Potent and moderate CYP3A inducers (eg, avasimibe, bosentan, carbamazepine, efavirenz, etravirine, modafinil, nafcillin, phenytoin, rifampin, St. John's wort);
- P-gp substrates (eg, digoxin);
- (Medical grade) marijuana, regardless of medical indication.

- Participants ***must not take the following medications on Day 1*** of this study:
  - Moderate CYP3A inhibitors (eg, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, fluconazole, fosamprenavir, imatinib);
  - Sensitive CYP2C9 substrates and substrates with a narrow therapeutic range (eg, fluvastatin, diclofenac, celecoxib, torsemide, warfarin, phenytoin).
- Participants ***must not take a morning dose of the following medications on Day 1*** of this study:
  - OCT2/MATE1 substrates (eg, metformin);
  - BCRP substrates (eg, rosuvastatin, atorvastatin, simvastatin, fluvastatin).

Herbal supplements must be discontinued ***at least 28 days*** prior to Day 1 and until the follow-up contact.

6.5.3. Rescue Medicine

There is no rescue therapy to reverse the adverse events (AEs) observed with PF-06865571; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

By design, this study only includes administration of a single, oral dose of PF-06865571. As such, dose modifications will not be made during the study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant who was dosed on Day 1 to permanently discontinue from the study. In such circumstances, procedures outlined under early termination visit in the Schedule of Activities Table must be attempted.

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

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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

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

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

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

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

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

Withdrawal of Consent:

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

publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow up

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

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 28 days prior to administration of the investigational product to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures. 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.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. C
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[redacted]

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

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

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

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

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 intravenous (IV) catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate 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 175 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 300 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 concerns.

8.2.1. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation as defined in the Schedule of Activities.

- A ***full physical examination*** will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems.

- A ***limited physical examination*** will be focused on general appearance, the respiratory, cardiovascular, and neurological systems, as well as towards participant reported symptoms, performed at Investigator discretion.

For measuring body 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

Blood pressure and pulse rate will be measured as defined in the Schedule of Activities. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

- **Single, seated** blood pressure/pulse rate will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mmHg, following a rest of **≥5 minutes;**

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

- Blood pressure/pulse rate assessment should not be taken from the arm with an intravenous catheter, if placed;

- Participants should be instructed not to speak during blood pressure/pulse rate 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 pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

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

8.2.3. Electrocardiograms

Supine 12-lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex. 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 QTcF interval is increased by ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTcF 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 QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

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

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

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

8.2.4. 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.

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 5 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

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

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

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Urine pregnancy tests will be performed in women of childbearing potential (WOCBP) at the times listed in the SoA, onsite. In addition, blood sample will be analyzed by the sponsor-identified central laboratory, in all females consented in this study. In WOCBP, following a negative pregnancy test result at screening, appropriate contraception must continue ***or*** be commenced and a second negative pregnancy test result will be required at the baseline visit (ie, urine testing on Day 1) prior to the participant's receiving the investigational product. 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 institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. On Day 1, if a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required with results reported by the sponsor-identified central laboratory; and in this case, dosing with PF-06865571 must be delayed. The participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

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 investigational product), through and including a ***minimum of 28 calendar days*** after the last administration of the investigational product.

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants or female partners of male participants will be collected after the start of study intervention and until the follow-up contact.

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

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

8.3.5.2. Exposure During Breastfeeding

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Medication Errors

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

Exposures to the investigational product 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 investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-06865571 greater than 1800 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/treating physician should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until PF-06865571 can no longer be detected systemically (at least 5 days).
3. 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).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety **only when associated with an SAE.**

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

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-06865571

Blood samples of approximately 4 mL, to provide approximately 1.5 mL plasma, will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) for measurement of plasma concentrations of PF-06865571 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 PK samples up to and including 8 hours after dose administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) 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 data collection tool (eg, CRF/DCT).

Samples collected at nominal times of ≥10 hours post dose must be collected within ±1 hour of the planned sampling time (eg, 16H sample can be collected as early as 15H post dose and as late as 17H post dose) and such not considered as protocol deviations, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF/DCT).

Samples will be used to evaluate the PK of PF-06865571. PK samples 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, CCI [redacted] These data will not be included in the clinical study report (CSR).

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

Samples collected for measurement of plasma concentrations of PF-06865571 will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs). 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. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters are not evaluated in this study.

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (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 24 participants (approximately 6 participants per cohort, with varying degrees of hepatic function in each of 4 cohorts) has sufficient power to detect a 2-fold difference from the Reference (without hepatic impairment) cohort. These calculations are based on estimates of between-participant standard deviations of 0.19 for $\log_e AUC_{inf}$ and 0.17 for $\log_e C_{max}$. These estimates were derived from single doses between 5 mg and 1500 mg administered in the fed state and one dose of 1000 mg administered in the

fasted state in Study C2541001. Table 2 presents the 90% confidence intervals (with 80% tolerance probability) for various possible effects.

Table 2. 90% Confidence Intervals (With 80% Tolerance Probability) for Various Possible Effects in AUC_{inf} and C_{max} With n=6 Participants/Cohort

Parameter	Estimated Fold Effect (Test/Reference)	Expected 90% CI
AUC_{inf}	0.5	0.40, 0.62
	1	0.81, 1.24
	2	1.62, 2.47
	4	3.24, 4.94
C_{max}	0.5	0.41, 0.60
	1	0.83, 1.21
	2	1.65, 2.42
	4	3.31, 4.83

9.3. Populations for Analysis

Population	Description
Enrolled	All participants who sign the ICD
Dosed with investigational product	All participants dosed with investigational product
Safety	All participants who take at least 1 dose of investigational product.

9.4. Statistical Analyses

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

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.4.2. Pharmacokinetic Analyses

9.4.2.1. Pharmacokinetic Analysis Populations

The PK concentration population will be defined as all participants who received PF-06865571 and in whom at least 1 plasma concentration value is reported.

The PK parameter analysis population is defined as all participants dosed who have at least 1 of the PK parameters of primary interest.

9.4.2.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

The plasma PK parameters for PF-06865571 following single 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. Plasma PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method.
AUC_{inf}*	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum plasma concentration	Observed directly from data.
CCI	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
*As data permit		

9.4.2.3. Statistical Methods for Pharmacokinetic Data

Individual PF-06865571 concentrations will be listed and summarized descriptively by nominal PK sampling time and hepatic function cohort. Individual and summary profiles of the concentration-time data will be plotted by hepatic function cohort. PF-06865571 AUC_{inf}, AUC_{last}, and C_{max} mean and individual parameters will be plotted by hepatic function cohort. PK parameters of PF-06865571 will be summarized descriptively by hepatic function cohort.

The effect of varying degrees of hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between each of the Test (impaired) cohorts and the Reference (without hepatic impairment) cohort. A 1-way analysis of variance (ANOVA) will be used to compare the natural log transformed PF-06865571 AUC_{inf}, AUC_{last}, and C_{max}, as data permit, for each of the hepatic impairment cohorts (Test) to the cohort without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test - Reference), and corresponding 90% confidence intervals, will be obtained from the model. These will be exponentiated to provide estimates of the

ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

CCI [redacted]

CCI [redacted]

9.4.3. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Secondary	The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include: • Treatment-emergent AEs; • Clinical laboratory tests; • Vital signs; • 12-lead ECGs.

9.4.3.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

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

CCI [redacted]

9.5. Interim Analyses

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

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

A copy of the ICD(s) must be provided to the participant.

CCI [redacted] 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. CCI [redacted] Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the investigator site file.

10.1.8. Study and Site Closure

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. 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 clinical laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

The clinical safety laboratory tests outlined in Table 10.2-1 will be performed *by the sponsor-identified central laboratory*. Blood and urine samples for clinical laboratory tests will be collected following ≥4-hour fast.

Table 10.2-1. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Reticulocyte count (Abs) MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine (***and*** eGFR via MDRD) Glucose (fasting) Calcium Sodium Potassium Chloride Phosphorus Total CO_2 (Bicarbonate) AST ALT Alkaline phosphatase GGT Total bilirubin Direct bilirubin[a,b] Indirect bilirubin[a,b] Creatine kinase[a,c] Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[d]	Other tests as part of clinical laboratory tests: • aPTT, PT, PT control, INR • Serum FSH[e] • Serum[f] and urine[f] pregnancy test • Breath alcohol test[g] • Urine drug test[h] • Serology[i] HBsAg, HCVAb (and if positive, reflex HCV RNA), and HIV
Additional Tests (Needed for Hy's law)			
AST ALT Total bilirubin Albumin Alkaline phosphatase Direct bilirubin	Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug levels and/or protein adduct level		

a. At Screening and Day 1, ***only.***
b. *After* Day 1, direct and indirect bilirubin assessed when total bilirubin is > ULN, ***only.***
c. *After* Day 1, creatine kinase assessed when ALT is > ULN, ***only***.
d. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
e. To be assessed in ***all*** females (at Screening ***only).***
f. Serum testing in ***all*** females at all times when safety-related laboratory assessments are performed; urine testing to be done on-site using kits provided by sponsor-identified central laboratory, in WOCBP, ***only***
g. Testing to be performed on-site, at Screening and Day -1, ***only*** using kits provided by sponsor-identified central laboratory
h. Minimum requirements include cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.
i. At Screening, ***only***.

For list of abbreviations, refer to Section 10.9.

Investigators must document their review of each laboratory safety report as soon as practically possible post receipt from sponsor-identified central laboratory. Results from Screening visit must be reviewed to confirm eligibility ***before*** progressing with dosing on Day 1.

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

10.3.1. Definition of AE

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the

participant's condition.

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

10.3.2. Definition of SAE

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

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

c. Results in death

d. 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.

e. 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.

f. 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.
g. Is a congenital anomaly/birth defect
h. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None

Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

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

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as

possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

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

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for ***at least 28 days*** after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

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

  OR

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

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

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not 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 study intervention(s).

- A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. 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 (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

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

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

2. Postmenopausal female.

    - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion.
5. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the 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.

Highly Effective Methods That Are User Dependent (WOCBP partners of male participants only)

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
2. Progestogen-only hormone contraception associated with inhibition of ovulation.
    - Oral;
    - Injectable.
3. Sexual abstinence.
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Collection of Pregnancy Information

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

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

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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

CCI [redacted]

[redacted]

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 beats per minute [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) atrioventricular (AV) block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free 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 (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

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

ECG Findings That Qualify as Serious Adverse Events

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

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

10.8. Appendix 8: Child-Pugh Classification (CPC) of Liver Dysfunction

Table 10.8-1: Scoring for Child-Pugh Classification

Cohort	CPC	Level of dysfunction	Total Score (tally based on assessment of parameters in **Table 10.8-2**)
1	Not Applicable	Without hepatic impairment	Not Applicable
2	A	Mild	5-6
3	B	Moderate	7-9
4	C	Severe	≥10

Table 10.8-2: Derivation of Child-Pugh Classification Score

Assessment Parameters	Assigned score for observed findings		
	1 point	2 points	3 points
Encephalopathy grade[a] (refer to **Table 10.8-3** below)	0	1 or 2	3 or 4[a]
Ascites	Absent	Asymptomatic	Requiring intervention
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged[b]	<4	4 to 6	>6

a. Subjects with a prior history of Grade 3 or Grade 4 encephalopathy who are ***currently*** receiving an intervention [*for example*: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to manage encephalopathy-related signs and symptoms should be scored for encephalopathy grading ***based on their presentation while on intervention at the Screening visit*** and can be included in this study as long as they do ***not*** have clinically active Grade 3 or Grade 4 encephalopathy.

b. As assessed relative to PT control (***or*** upper limit of normal), as reported by sponsor-identified central laboratory

Table 10.8-3: Determination of Encephalopathy Grade

Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia
3[a]	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
4[a]	Unrousable coma, no personality/behavior, decerebrate

a. Subjects with clinically active Grade 3 or 4 encephalopathy are excluded.

CPC should be assessed *at Screening only* to determine the classification of a given participant.

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADME	absorption, distribution, metabolism, or excretion
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration-time profile from 0 to 24 hours
AV	atrioventricular
BA	bioavailability
CCI	[redacted]
BCRP	breast cancer resistance protein
BE	bioequivalence
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
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
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CPC	Child-Pugh classification
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
CV	cardiovascular
CYP	cytochrome P450
DAG	diacylglycerol
DBP	diastolic blood pressure
DC	discontinuation
DCT	data collection tool
DDI	drug-drug interactions
DGATs	Diacylglycerol acyltransferases
DILI	drug-induced liver injury
DMC	data monitoring committee
CCI	[redacted]
DNL	de novo lipogenesis

Abbreviation	Term
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FA	fatty acid
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCVAb	Hepatitis C antibody
HCV RNA	Hepatitis C ribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IR	immediate release
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWR	interactive Web-based response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LFT	liver function test
MATE	multidrug and toxic compound extrusion transporter
mBcrp	mouse breast cancer resistance protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multi-drug resistance protein
MDRD	Modification of Diet in Renal Disease
MR	modified release
MRI	magnetic resonance imaging
msec	millisecond
N/A	not applicable

Abbreviation	Term
NAb	neutralizing antibodies
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NOAEL	no-observed-adverse-effect level
OCT	organic cation transporter
PBMC1	peripheral blood mononuclear cells
PCD	primary completion date
PD	pharmacodynamic(s)
PE	physical exam
P-gp	P-glycoprotein
CCI	[redacted]
PI	principal investigator
PIB	powder in bottle
PK	pharmacokinetic(s)
PT	prothrombin time
PVC	premature ventricular contraction/complex
Q8H	every 8 hours
Q12H	every 12 hours
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSID	study-specific identification
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TBili	total bilirubin
TG	triglyceride
THC	tetrahydrocannabinol
TIPS	transjugular intrahepatic portosystemic shunt
UGT	uridine diphosphate-glucuronosytransferase
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	woman of childbearing potential

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