A PHASE 1, RANDOMIZED, OPEN-LABEL, 3-PERIOD, CROSSOVER, SINGLE-DOSE, 2-PART STUDY IN HEALTHY PARTICIPANTS TO INVESTIGATE THE EFFECT OF TABLET FORMULATION AND FOOD ON THE RELATIVE BIOAVAILABILITY OF PF-06821497

Study Intervention Number:	PF-06821497
Study Intervention Name:	NA
US IND Number:	CCI [redacted]
EudraCT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C2321005
Phase:	Phase 1
Brief Title: A Phase 1, Single-dose, Relative Bioavailability Study to Investigate the Effect of Tablet Formulation and Food on PF-06821497 Pharmacokinetics in Healthy Participants.	

Document History

Document	Version Date
Original protocol	02 Feb 2023

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Open-label, 3-period, crossover, single-dose, 2-part study in healthy participants to investigate the effect of tablet formulation and food on the bioavailability of PF-06821497

Brief Title: A Phase 1, Single-dose, Relative Bioavaialbility Study to Investigate the Effect of Tablet Formulation and Food on PF-06821497 Pharmacokinetics in Healthy Participants

Regulatory Agency Identification Number(s):

US IND Number:	CCI
EudraCT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C2321005
Phase:	Phase 1

Rationale:

The purpose of the study is to investigate the relative bioavailability of tablet formulations of PF-06821497 and to characterize the effect of food on a PF-06821497 CCI tablet formulation (Formulation 2). The data generated from this study will be used to support the pivotal study formulation, to inform dose administration instructions for PF-06821497 with regard to dosing with or without food, and to enable the establishment of the API particle size specifications for eventual commercialization.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the bioavailability of a single C mg dose of PF-06821497 CC tablet formulation (Formulation 2) relative to a single C mg dose of PF-06821497 CCI tablet formulation (Formulation 1) under fasted conditions in adult healthy participants	• Plasma AUC_{inf} and C_{max} for PF-06821497. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
Secondary:	**Secondary:**
• To estimate the bioavailability of a single C mg dose of PF-06821497 CC tablet (larger API particle size) formulation (Formulation 3) relative to a single C mg dose of PF-06821497 CC tablet (Formulation 2) and a single C mg dose of the PF-06821497 CCI tablet formulation (Formulation 1) under fasted conditions in adult healthy participants	• Plasma AUC_{inf} and C_{max} for PF-06821497 for CC tablet (larger API particle size) (Formulation 3) relative to CC (Formulation 2) and CCI tablet (Formulation 1) formulations. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).

Objectives	Endpoints
• To estimate the effect of a high-fat, high-calorie meal on the bioavailability of a single CCI mg dose of the PF-06821497 CC tablet formulation (Formulation 2) relative to fasted conditions in adult healthy participants • To estimate the effect of a low-fat, low-calorie meal on the bioavailability of a single CCI mg dose of the PF-06821497 CC tablet formulation (Formulation 2) relative to fasted conditions in adult healthy participants	• Plasma AUC_{inf} and C_{max} for PF-06821497 under fed (high-fat, high-calorie meal) conditions relative to fasting conditions. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated). • Plasma AUC_{inf} and C_{max} for PF-06821497 under fed (low-fat, low-calorie meal) conditions relative to fasting conditions. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
• To evaluate the safety and tolerability of PF-06821497 when administered as a tablet formulation to healthy participants	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, physical examinations, and 12-lead ECGs.

Overall Design:

This is a Phase 1, randomized, open-label, 3-period, single-dose 2-part study in healthy adult participants to investigate the effect of tablet formulation and food on the bioavailability of PF-06821497.

Intervention Groups and Duration:

Part 1 (rBA):

Sequence	Period 1	Washout: at least C days between PF-06821497 doses	Period 2	Washout: at least C days between PF-06821497 doses	Period 3
1 (6 Participants)	A		B		C
2 (6 Participants)	B		A		C

Treatment A – CCI formulation (Formulation 1) [redacted] fasted;
Treatment B – CC formulation (Formulation 2) [redacted] fasted;
Treatment C – CC formulation (Formulation 3) [redacted]; larger particle size) fasted ;

Part 2 (Food effect):

Sequence	Period 1	Washout: at least C days between PF-06821497 doses	Period 2	Washout: at least C days between PF-06821497 doses	Period 3
1 (6 Participants)	D		E		F

Treatment D – CC formulation ((Formulation 2) [redacted] fasted;
Treatment E – CC formulation (Formulation 2) [redacted] fed: Low-fat meal;
Treatment F – CC formulation (Formulation 2) [redacted] fed: High-fat meal

There will be a minimum of CCI washout period between successive PF-06821497 doses.

Blood samples for PF-06821497 PK analysis will be collected predose and at CCI post the PF-06821497 dose in each period.

In each part, participants will be on the study up to 10 weeks, including the screening and follow-up periods. Participants will be screened within 28 days prior to the first dose of the IP and if all entry criteria are fulfilled, the participants will report to the PCRU on the day prior to Day 1 dosing (Day -1) of each period. For Treatments A, B, and C, following an overnight fast of at least 10 hours, and after the collection of the pre-dose PF-06821497 PK sample on Day 1 of each period, participants will be administered a CCI mg dose of PF-06821497. For Treatment D, following an overnight fast of at least 10 hours, and after the collection of the pre-dose PF-06821497 PK sample on Day 1 of each period, participants will be administered a CCI mg dose of PF-06821497. For Treatment E, after an overnight fast of at least 10 hours and after the collection of pre-dose PF-06821497 PK sample on Day 1, participants will receive a low-fat, low-calorie breakfast 30 minutes prior to dosing. For Treatment F, after an overnight fast of at least 10 hours and after the collection of pre-dose PF-06821497 PK sample on Day 1, participants will receive a high-fat, high-calorie breakfast 30 minutes prior to dosing. Participants are strongly encouraged to consume the breakfast in its entirety. PF-06821497 will be administered as intact tablets with approximately 240 mL of ambient temperature water. Tablets will be swallowed and not chewed.

In Part 2 of the study, before the Period 3 doses are administered to participants that have eaten a high-fat meal, the safety data for Period 2, including at least 3 participants administered a low-fat meal in Period 2, will be reviewed by the study team and the investigator and assessed based on safety and tolerability. Period 3 will initiate as planned if the doses administered in Period 2 were well-tolerated.

Following administration of PF-06821497, participants will be confined in the PCRU for a minimum of C days until completion of the CCI PK sample collection and discharge assessments on Day C in each period, or at the discretion of the investigator participants could remain admitte C d to the PCRU throughout study conduct and discharged on Day C of Period 3 in each part. Participants will be discharged at the discretion of the investigator. A follow-up phone call will be made at least 28 calendar days and up to 35 calendar days after the last administration of study intervention to capture any potential AEs and confirm appropriate contraceptive usage.

Number of Participants:

Approximately 18 participants will be enrolled to the study intervention. If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective(s), additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants

who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Participants ≥18 years of age, inclusive, at screening.

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs and 12-lead ECGs.

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

4. Evidence of a personally signed and dated ICD indicating that the participant has been informed of all pertinent aspects of the study.

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

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing) or prior allergic reaction to any component of PF-06821497.

    - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy, prior bariatric surgery, ileal resection, inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease).

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAB or HCVAb. Hepatitis B vaccination is allowed.

    - Chronic liver diseases including alcoholic liver disease, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune

hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, human immunodeficiency virus, or other chronic liver disease.

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

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

    - Current use or anticipated need for food or drugs that are known strong inducers or inhibitors of CYP3A4/5, including their administration within 10 days or 5 half-lives of the strong inducer or inhibitor of CYP3A4/5, whichever is longer prior to first dose of investigational product

        - Strong CYP3A4/5 inhibitors: eg, grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan.

        - Strong CYP3A4/5 inducers: eg, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St. John's Wort.

    - Time dependent inhibitors of CYP3A4/5 for atleast 21 days prior to the treatment
        - Time dependent inhibitors of CYP3A4/5: azamulin, troleandomycin, verapamil, boceprevir, nelfinavir, and telapravir

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

5. A positive urine drug test.

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

7. Standard 12 lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.

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

    - AST or ALT level > ULN;
    - Total bilirubin level >1 × ULN;
    - PT, international normalized ratio (INR) and aPTT outside of normal limits at baseline
    - eGFR <60 mL/min/1.73 m2 based on the CKD-EPI equation;
    - Absolute neutrophil count <0.8 × LLN.

9. History of alcohol abuse or binge drinking [more than 4 drinks on any day or 14 drinks per week where 1 drink is defined as the alcoholic beverage containing approximately (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine)] in the last 6 months prior to study screening.

10. Use of tobacco or nicotine containing products within 3 months of screening or a positive urine cotinine test (ie, active smokers and those who currently use nicotine containing products are excluded from participation in this study).

11. Pregnant female participants; breastfeeding female participants; fertile male participants and female participants of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 3 months after the last dose of investigational product.

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

13. History of sensitivity to heparin or heparin induced thrombocytopenia.

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

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

Study Arms and Duration:

Each participant will be screened within 28 days prior to the first dose of the IP and if all entry criteria are fulfilled, the participants will report to the PCRU on the day prior to Day 1

dosing (Day -1) of each period. A safety follow-up call will be made to participants 28 to 35 days from administration of the final dose of study intervention.

In each part of the study, each enrolled participant will participate in 3 study periods to receive 3 different treatments according to the sequence determined by randomization with C-day washouts between PF-06821497 administration:

Part 1:

- Treatment A – CCI formulation (Formulation 1) CCI fasted;
- Treatment B – CCI formulation (Formulation 2) CCI fasted;
- Treatment C – CCI formulation (Formulation 3) CCI ; larger API particle size) fasted;

Part 2:

- Treatment D – CCI formulation (Formulation 2) CCI fasted;
- Treatment E – CCI formulation (Formulation 2) CCI fed: Low-fat meal;
- Treatment F – CCI formulation (Formulation 2) CCI fed: High-fat meal;

Statistical Methods:

Part 1:

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A (CCI formulation (Formulation 1) CCI fasted) will be the Reference treatment and Treatment B (CCI formulation (Formulation 2) CCI fasted) will be the Test treatment.

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A (CCI formulation (Formulation 1) CCI

CCI fasted) will be the Reference treatment and Treatment C (CCI formulation (Formulation 3) CCI ; larger API particle size) fasted) will be the Test treatment. For the second comparison, Treatment B (CCI formulation (Formulation 2) CCI will be the Reference treatment and Treatment C (CCI formulation (Formulation 3) CCI ; larger API particle size) fasted) will be the Test treatment.

Part 2:

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment D (CCI formulation (Formulation 2) CCI fasted) will be the Reference treatment and Treatments E and F (CCI formulation (Formulation 2) 1250 mg CCI fed: low-fat meal and CCI formulation (Formulation 2) CCI fed: high-fat meal) will be the Test treatments.

Pharmacokinetics Analysis

The PK concentration population is defined as all participants randomized and treated who have at least 1 PF-06821497 concentration in at least 1 treatment period.

The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PF-06821497 PK parameters of primary interest in at least 1 treatment period.

PK parameters for PF-06821497 will be analyzed using standard noncompartmental methods of analysis. Actual PK sampling times will be used in the derivation of PF-06821497 PK parameters when available, otherwise nominal times will be used. The PF-06821497 plasma PK parameters will be summarized descriptively by Treatment. Plasma concentrations will be listed and summarized descriptively by Treatment, and nominal PK sampling time. Individual participant and summary profiles (mean and median plots) of the plasma concentration time data will be plotted using actual and nominal times, respectively.

Safety Analysis

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

Ethical Considerations:

PF-06821497 will not provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of PF-06821497. Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	**Screening**	**Period 1 to Period 3**															**F/U**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**													CCI	**28-35 Days**		• Screening will be performed within 28 days prior to the first dose of PF-06821497. • Day -1 is applicable for each check-in to the PCRU, unless particularly specified. • Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention
Hours After Dose			**Pre-dose**	**0**	CCI														
Informed consent	X																		• Informed consent should be obtained prior to undergoing any study-specific procedures • See Section 10.1.3 for additional information.
CRU confinement		X														C			• Participants will be admitted to the PCRU on Day -1 of each period. Participants may be discharged on Day C of each period at the discretion of the investigator following the completion of all Day C assessments, or at the discretion of the investigator participants could remain admitted to the PCRU throughout study conduct and discharged on Day C of Period 3.
Inclusion/exclusion criteria	X	X																	• Inclusion/exclusion criteria will be reviewed at Screening and at the Day -1 check-in for Period 1.
Medical/medication history	X	X																	• Medical history will include a history of prior illegal drug, alcohol, and tobacco use and will be recorded at Screening and updated on Period 1 Day -1.

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	**Screening**	**Period 1 to Period 3**														**F/U**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**											**Day 2**	**Day 3**	**28-35 Days**		• Screening will be performed within 28 days prior to the first dose of PF-06821497. • Day -1 is applicable for each check-in to the PCRU, unless particularly specified. • Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention
Hours After Dose			**Pre-dose**	**0**	[redacted]													
Physical exam	X	X															X	• A completed physical examination will be performed by trained medical personnel at the PCRU at Screening or Period 1 Day -1 only (height and weight must be obtained at Screening to obtain BMI for eligibility criteria). Additional physical examination may be performed at other designated time points at the discretion of the investigator.
PT, PTT, INR	X	X													X		X	
Safety laboratory	X	X													X		X	• Safety laboratory assessments will be performed at Screening, prior to dosing in each treatment period (can be Day -1 or pre-dose on Day 1 at discretion of investigator), and prior to each discharge from the PCRU (could be Day C in each period or only at Day C of Period 3 at discretion of investigator), and prior to early termination/discontinuation if applicable. All the safety laboratory samples must be collected following at least a 4 hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator (see Appendix 2)
Demography	X																	• Demographics will include participant race, ethnicity, age, sex, height, and weight during the Screening visit.
Pregnancy test (WOCBP only)	X	X													X		X	• For Day C it is only applicable for Period 3 (See Section 8.3.6).
Contraception check	X	X														X	X	• Contraception check will be performed according to the conditions described in Section 5.3.1
FSH	X																	• For postmenopausal (amenorrheic for at least 12 consecutive months) female participants only

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	**Screening**	**Period 1 to Period 3**													**F/U**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**										CCI		**28-35 Days**		• Screening will be performed within 28 days prior to the first dose of PF-06821497. • Day -1 is applicable for each check-in to the PCRU, unless particularly specified. • Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention
Hours After Dose			**Pre-dose**	**0**	[redacted]												
Urine drug screening/Urine cotinine/Alcohol breath test	X	X															• Urine drug and urine cotinine (mandatory) and alcohol breath test (at discretion of investigator) will be performed at Screening, on Period 1 Day -1, and upon PCRU check-in on Day -1 of each subsequent period. These tests may be performed at any other time at the discretion of the investigator.
12-Lead ECG	X		X					C								X	• Single 12-lead ECG readings will be taken at approximately the specified time point. All ECG assessments will be made after at least a 5 minute rest in a supine position and prior to any blood draws or vital sign measurements. Additional ECGs may be taken at any time at the discretion of the investigator. • Single 12-lead ECG monitoring will be done pre-dose of Day 1 of each treatment period. • Chour post-dose ECG readings are applicable only for Periods 2 and 3 in Part 2. Day Cmeasurements are for Period 3 only.
Vital signs (BP/PR/RR and temperature)	X		X					C								X	• Single supine BP, RR and PR will be performed following at least a 5 minute rest in a supine position, at specified time point. BP, RR and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. • Vital sign measurements will be done pre-dose of Day 1 of each treatment period. • Chour post-dose vital sign measurements are applicable only for Periods 2 and 3 in Part 2. Day Cmeasurements are for Period 3 only.

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	**Screening**	**Period 1 to Period 3**													**F/U**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**											CCI	**28-35 Days**		• Screening will be performed within 28 days prior to the first dose of PF-06821497. • Day -1 is applicable for each check-in to the PCRU, unless particularly specified. • Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention
Hours After Dose			**Pre-dose**	**0**	CCI												
HIV, HBsAg, HBcAb, HCVAb	X																
COVID-19 related measures	X	X															• The measures will be according to PCRU procedures.
COVID-19 testing	X	X															• The testing for COVID-19 will be performed per PCRU procedures or by the Principal Investigator.
PF-06821497 dosing				X													• PF-06821497 will be administered orally on Day 1 after overnight fasting until the start of study procedures for each treatment period. PF-06821497 will be administered orally and in fasted or fed state according to the conditions described in Protocol Section 5.3.2.
Pharmacokinetic blood sampling for PF-06821497			X		CCI											X	• Blood samples (~2 mL) for PK analysis of PF-06821497 will be taken at predose (within approximately 1 hour prior to PF-06821497 dosing), and at the specified timepoints post dose. If ECG and BP/PR assessments are scheduled at the same nominal time point as a PK sample, PK samples should be collected after completion of these assessments. A 10% time window is allowable for samples collected upto CCI . ≤ 1hour is allowed for samples collected at more than CCI
CCI																	

Visit Identifier Abbreviations used in this table may be found in Appendix 9.	**Screening**	**Period 1 to Period 3**			**F/U**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	CCI	**28-35 Days**		• Screening will be performed within 28 days prior to the first dose of PF-06821497. • Day -1 is applicable for each check-in to the PCRU, unless particularly specified. • Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention
Hours After Dose			**Pre-dose**	**0** CCI			
CRU discharge				C			• CRU discharge will be applicable for discharge day from the PCRU (could be Day C in each period or only at Day C of Period 3 at discretion of investigator, and prior to early termination/discontinuation if applicable).
Serious and nonserious AE monitoring	X	→	→		C	X	• See Section 8.4.3 for follow-up AE and SAE assessments.

2. INTRODUCTION

PF-06821497 is a potent and selective inhibitor of EZH2 as evidenced by its biochemical inhibition of both WT and EZH2 Y641N mutant enzymes. PF-06821497 is currently being proposed for investigation in patients with SCLC, CRPC, DLBCL, and FL.

2.1. Study Rationale

The purpose of the study is to investigate the relative bioavailability of tablet formulations of PF-06821497 and to characterize the effect of food on a PF-06821497 CCI tablet formulation (Formulation 2). The data generated from this study will be used to support the pivotal study formulation, to inform dose administration instructions for PF-06821497 with regard to dosing with or without food, and to enable the establishment of the API particle size specifications for eventual commercialization.

2.2. Background

The histone methyltransferase EZH2 is the catalytic subunit of the PRC2 which methylates lysine 27 on histone H3 leading to repression of gene transcription. PF-06821497 is a potent and selective small molecule inhibitor of EZH2 as evidenced by its biochemical inhibition of both WT and EZH2 Y641N mutant enzymes. PF-06821497 is currently being proposed for investigation in patients with SCLC, CRPC, and FL. To date, clinical drug supplies of PF-06821497 have used the CCI tablet formulation, CCI [redacted]. As the clinical development program of PF-06821497 is preparing to move to later stages of development, activities are underway to further develop and optimize the manufactured PF-06821497 drug product.

PF-06821497 has relatively CCI [redacted] Based on the solubility and permeability data collected in the pre-clinical phase, PF-06821497 is considered to be a CCI drug. For this class of compound, food is CCI to show a CCI [redacted] Following single-dose oral administration as a suspension in dogs, oral bioavailability was higher in a fed state than in a fasted state. CCI [redacted]

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-06821497 can be found in the current IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

PF-06821497 exhibited CCI CL_p and a moderate V_{ss} in rats and dogs. Renal excretion was low in rats and dogs, and biliary excretion was CCI in rats. Following oral administration, PF-06821497 was rapidly absorbed with CCI oral bioavailability in rats and CCI oral bioavailability in dogs. Following single-dose oral administration as a suspension in dogs, oral bioavailability was CCI in a fed state than in a fasted state, suggesting a potential food effect in the clinic. In oral repeat dose toxicity studies in mice and dogs, the systemic exposure of PF-06821497 generally CCI in a CCI CCI up to CCI kg/kg/day (CCI mg/kg/dose BID) with no consistent sex-related differences

observed. CCI accumulation CCI was observed over the dosing period. PF-06821497 is a CCI of the CCI ; however, nonclinical in vivo PK results suggested a CCI impact of CCI on intestinal absorption.

PF-06821497 showed CCI plasma protein binding with f_u in plasma of CCI across species tested and partitioning of PF-06821497 into blood cells was modest with blood to plasma ratios of CCI. Brain penetration of PF-06821497 was CCI in mice, with unbound brain to plasma AUC ratios of CCI. PF-06821497 distributed into human hepatocytes by CCI and showed the CCI for biliary excretion in sandwich cultured human hepatocytes.

Preliminary in vitro metabolism evaluation of PF-06821497 showed similar metabolite profiles across species with no evidence of human specific metabolites. PF-06821497 was primarily metabolized by CCI and CCI pathways via CYP and non-CYP mediated metabolism. CYP-mediated metabolism accounted for CCI of the hepatic metabolism with CCI and CCI the predominant CYP isoforms, whereas nCCI -mediated metabolism (CCI was due, in part, to CCI

PF-06821497 showed minimal reversible CCI of CCI PF-06821497 exhibited weak potential for time dependent inhibition of CCI, and weakly CCI in human hepatocytes. PF-06821497 showed minimal inhibition of CCI , and CCI Additionally, PF-06821497 weakly CCI in vitro. Based on in vitro data, PF-06821497 showed minimal inhibition of CCI , CCI , but may have the potential to inhibit CCI in humans at a predicted PAD of CCI mg PO BID PF-06821497.

Additional information of the nonclinical PK and metabolism of PF-06821497 is available in the current IB.

2.2.3. Nonclinical Safety

The nonclinical safety profile of PF-06821497 was adequately characterized through the conduct of oral, acute or repeat-dose mouse and dog oral toxicity studies up to 1 month in duration, as well as genetic toxicity studies. In the pivotal 1-month toxicity studies, the primary effects of PF-06821497 were observed in the dog, while no findings were detected in the mouse. The key toxicities identified in nonclinical safety studies were observed in the gastrointestinal tract (mucosal atrophy, congestion and erosion), hemato-lymphopoietic system (decreased cellularity in the bone marrow, myeloid and erythroid toxicity, decreased lymphocyte cellularity in the lymphoid organs), and male reproductive organs (seminiferous tubule degeneration and reduced sperm in epididymis). Partial to complete reversibility of target organ toxicities was established following a 1-month non-dosing period.

PF-06821497 was assessed in a series of exploratory genetic toxicity studies consisting of the bacterial mutagenicity, in vitro cytogenetic (micronucleus in human lymphoblastoid TK6 cells), a GLP bacterial mutagenicity assay, and a GLP in vivo mouse micronucleus assays.

All in vitro tests were conducted with and without exogenous metabolic activation using concentrations up to the limits recommended in the regulatory guidelines for the test system. PF-06821497 was not genotoxic in either in vitro or in vivo assays micronucleus study.

Reproductive and developmental toxicity studies with PF-06821497 have not been conducted. Effects on male and female reproductive system have been assessed as part of the repeat-dose toxicity studies in mice and dogs. EZH2 has been shown to be abundantly expressed during embryonic development and EZH2 knockout caused embryonic lethality[2] therefore, PF-06821497 is expected to have the potential to cause embryo-fetal toxicity.

PF-06821497 may have phototoxicity potential based on its molar extinction coefficients. In an investigative study of liver fibrosis in male mice, PF-06821497 did not increase or mitigate CCl4-induced liver toxicity.

Additional information of the nonclinical safety of PF-06821497 is available in the current IB.

2.2.4. Clinical Overview

PF-06821497 is currently being evaluated in an ongoing FIP open-label, multi-center, dose escalation and expanded cohort Phase 1 study (C2321001) to investigate the safety, tolerability, PK, PD, and preliminary efficacy of PF-06821497 as a single agent and in combination with SOC (Carboplatin or Cisplatin with etoposide for SCLC and enzalutamide for mCRPC) to patients with SCLC, mCRPC, and FL. The study is comprised of 2 parts: Part 1 testing PF-06821497 monotherapy in 3 arms (Part 1A, 1B, 1C) and Part 2 testing combination therapy in 3 parts (Part 2A, 2B, 2C). For Part 2, PF-06821497 in combination with SOC will be evaluated in dose escalation (Part 2A) in patients with SCLC and mCRPC and then the combination regimen will be evaluated in a randomized dose expansion in patients with mCRPC (Part 2B). Alternative doses of PF-06821497 in combination with SOC may be evaluated in patients with mCRPC (Part 2C).

2.2.5. 2.2.4.1 Safety Overview

Preliminary data from the ongoing study, C2321001, indicate that PF-06821497 as monotherapy and in combination with SOC has been well tolerated in doses from 75 mg to 1250 mg BID. As of 19 November 2021, PF-06821497 has been administered to 87 participants with advanced cancer in Study C2321001. Among the 87 participants with advanced cancer treated in Study C2321001 who received 75, 150, 250, 375, 500, 625, 750, 875, or 1250 mg BID of PF-06821497 either as single agent or in combination with SOC, 86 patients reported at least 1 TEAE. Among the 87 patients treated at the same dose levels either as single agent or in combination with SOC, 65 patients reported at least 1 TEAE considered to be treatment-related.

The most frequently reported (≥15%) all causality TEAEs across all the tumor types and dose groups in single agent or in combination with SOC regimens were anemia CCI, nausea CCI, thrombocytopenia CCI, diarrhea CCI, neutropenia CCI, fatigue CCI, decreased appetite CCI, leukopenia CCI, asthenia and alopecia CCI each), dysgeusia CCI, vomiting CCI, and arthralgia CCI. Note that 29 out of the

31 patients with SCLC treated in the study received PF-06821497 in combination with marrow toxic SOC backbones, which may have contributed to AEs of cytopenias.

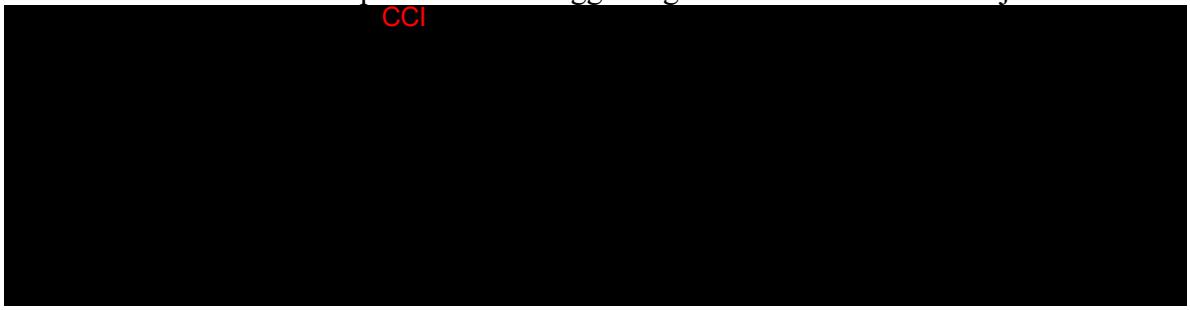
The most frequently reported (≥10%) PF-06821497 treatment related TEAEs across all the tumor types and dose groups were thrombocytopenia and nausea [redacted] each), anemia [redacted], neutropenia and diarrhea ([redacted] each), fatigue and decreased appetite [redacted] each), dysgeusia [redacted], leukopenia [redacted], and alopecia and vomiting ([redacted] each).

Across the study the majority of the TEAEs reported were Grade 2 or lower. Of the 87 patients, 23 (26.4%) patients reported Grade 3 TEAEs, 24 (27.6%) patients reported Grade 4 TEAEs and 4 (4.6%) patients reported Grade 5 TEAEs. Of these TEAEs, 14 patients experienced Grade 3 TEAEs (16.1%) and 9 patients experienced Grade 4 TEAEs (10.3%) that were deemed related to study drug (PF-06821497).

Across the study there were 52 SAEs (all-causality) reported in 33 participants. Of these 13 SAEs reported in 7 patients were considered to be treatment related. SAEs reported were hepatic failure and sepsis (in one patient), thrombocytopenia and hemorrhagic disorder (in one patient), acute coronary syndrome (in one patient), febrile neutropenia and pancytopenia (in one patient), thrombocytopenia and haemorrhage (in one patient), anemia (in one patient) and electrocardiogram QT prolongation and presyncope (in one patient).

Across the study there were 12 deaths reported with eleven (11) deaths considered unrelated to study treatment. One (1) event of hepatic failure was considered to be treatment-related.

The event of hepatic failure was reported during the trial and was considered to be treatment-related. Hepatic failure with a fatal outcome occurred in a [redacted] subject with CRPC enrolled in Cohort 2 (150 mg BID, single agent treatment of PF-06821497) who also developed significant increases in ALT, AST, bilirubin, and alkaline phosphatase associated with hepatic failure and sepsis. The etiology of hepatic failure is unclear. Liver transaminases, bilirubin, and alkaline phosphatase were initially normal at baseline, and began to significantly increase approximately 3 months after starting oral administration of PF-06821497 and remained elevated, along with subsequent development of increased PT and PTT, at time of death 2 months later. Shortly prior to the time of death, subject also developed pneumonia and sepsis. Much of the diagnostic work up including imaging and ERCP was inconclusive. The liver biopsy showed minimal hepatocellular injury or loss, and no evidence of extensive hepatic necrosis suggesting cholestasis as a cause of jaundice rather



06821497 based on the mechanism of action and the toxicology observations in the non-clinical studies. PF-06821497 exposures in this patient after first and multiple doses in Cycle

1 did not appear to differ markedly from the other patients in this 150 mg BID dose cohort. Considering the plausible drug-event temporal association and the provided clinical course of this event, including results of extensive lab tests, imaging, ERCP, liver biopsy, lacking at present alternative explanations, the reported liver failure is assessed as possibly related to PF-06821497. In conclusion, subject PPD developed cholestatic jaundice during the terminal course while receiving PF-06821497. Since the study drug is temporally associated, the possibility of a cholestatic reaction cannot be entirely excluded, but the presence of multiple other factors makes it impossible to attribute a definite cause in this case. This patient, along with the 86 other patients dosed (by the IB version 6 data cut off of 19 Nov 2021) in the FIH study received PF-06821497 BID in continuous 21-day cycles. No other cases of confirmed or suspected treatment-related hepatic failure have been reported for PF-06821497. As of the CTSUR/DSUR data cut off of 19 Dec 2022, no new safety signals have been identified. Further details on the clinical safety information with PF-06821497 are provided in the current IB.

2.2.6. 2.2.4.2. Summary of PF-06821497 Pharmacokinetics in Humans

PK of PF-06821497 following the first dose (C1D1), and Day 15 morning dose (C1D15) are being evaluated in the ongoing study (C2321001). Preliminary NCA was conducted with draft concentration-time data (QC'd, non-QA'd) available as of 09 Nov 2021, using nominal times of sample collection and Phoenix WinNonlin version 8.2. Draft data of C1D1 and C1D15 from patients at 6 dose levels (75 to 625 mg BID) from Part 1A and 1B, 4 dose levels (150 to 500 mg BID) from Part 2A SCLC, and 8 dose levels (150 to 250 mg BID) Part 2A CRPC of the study. PF-06821497 was administered orally on an empty stomach conditions.

In Part 1A and Part 1B of C2321001, PF-06821497 was given as monotherapy in patients with SCLC, CRPC, and FL. After oral administration, PF-06821497 was CCI absorbed following doses ranging from 75 to 625 mg BID in monotherapy, with a median T_{max} ranging from CCI after single dose and CCI hours after multiple dosing. After achieving C_{max}, PF-06821497 appeared to have CCI decline with a CCI mean t1/2 ranging from CCI hours at single dose and CCI after multiple dosing. Both single dose AUC_{inf} and steady state AUC_{tau} exhibit CCI. The interpatient variability across dose levels (geometric %CV) for steady-state AUC_{tau} ranges from CCI

In Part 2A of C2321001, PF-06821497 was given in combination with chemotherapy (either carboplatin or cisplatin) to patients with SCLC. After oral administration, PF-06821497 was CCI absorbed following doses ranging from 150 to 500 mg BID in combination with chemotherapy, with a median T_{max} ranging from CCI hours after single dose and CCI hours after multiple dosing. After achieving C_{max}, PF-06821497 appeared to have multi-phasic decline with a short mean $t_{1/2}$ ranging from CCI hours at single dose and CCI after multiple dosing. When PF-06821497 was given in combination with chemotherapy, the PK parameters were CCI to the PK parameters for PF-06821497 in monotherapy, for each respective dose level.

In Part 2A of C2321001, PF-06821497 was given in combination with enzalutamide 160 mg QD to patients with CRPC. After oral administration, PF-06821497 was CCI absorbed

following doses ranging from 150 to 1250 mg BID in combination with enzalutamide 160 mg QD, with a median T_{max} ranging from [redacted] hours after single dose and [redacted] hours after multiple dosing. After achieving C_{max}, PF-06821497 appeared to have [redacted] decline with a [redacted] mean $t_{1/2}$ ranging from [redacted] hours at single dose and [redacted] after multiple dosing.

Enzalutamide 160 mg QD is a strong inducer of CYP3A (as well as other enzymes and transporters) and [redacted] PF-06821497 [redacted] exposure at steady state after multiple dosing as compared to single dose. There is an approximate [redacted] in PF-06821497 exposure (geometric mean steady state AUC_{tau}) when given as monotherapy as compared to when given in combination with enzalutamide at the same respective dose levels (150 mg BID to 500 mg BID).

Further details on the clinical PK of PF-06821497 are provided in the current IB.

2.3. Benefit/Risk Assessment

PF-06821497 will not provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of PF-06821497. Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.

Study C2321005 is the first time that PF-06821497 will be administered to healthy adult participants. Prior to this study, PF-06821497 has been administered as monotherapy or in combination with other anti-cancer agents to advanced cancer patients at doses ranging from 75 mg to 1250 mg BID continuously. Based on the results of the nonclinical toxicity studies (Section 2.2.3), the potential risk of PF-06821497 administration to healthy participants can be managed adequately, and be mitigated with preventive measures in place that includes routine monitoring of adverse events and changes in clinical laboratory test parameters for clinical management, including study drug discontinuation as appropriate to ensure the safety of the study participant. Based on the available data from Study C2321001, the clinical safety profile favors further development of PF-06821497.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06821497 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-06821497		
Potential of PF-06821497 to cause embryo-fetal and reproductive organ toxicity	Reproductive and developmental toxicity studies with PF-06821497 have not been conducted. Effects on male and female reproductive system have been assessed as part of the repeat-dose toxicity studies in mice and dogs. Male reproductive organ toxicities were observed in repeat dose studies, namely seminiferous tubule degeneration and reduced sperm in epididymis. EZH2 has been shown to be abundantly expressed during embryonic development and EZH2 knockout caused embryonic lethality, therefore, PF-06821497 is expected to have the potential to cause embryo-fetal toxicity.	Eligibility criteria and contraceptive lifestyle requirements for this protocol have been crafted to mitigate these identified potential risks (see Section 5).
Potential phototoxicity effects of PF-06821497	PF-06821497 absorbs in the UVA-UVB/visible range from 290 to 700 nm with a calculated MEC of >1000 L/(mol cm) and, as a result, could have photosafety risks.	The lifestyle guidelines for this protocol include participant instructions to limit exposure to sunlight/high intensity ultraviolet light and use sunscreen products with high sun protection factor.
Potential risks associated with PF-06821497 include the following: GI toxicities (nausea, diarrhea), hematological (thrombocytopenia, nausea, anemia, neutropenia,), hepatotoxicity, and fatigue, decreased appetite, dysgeusia	The potential risks are based on emerging clinical data from the ongoing study C2321001 following continuous administration of PF-06821497 to advanced cancer patients at doses ranging from 75 to 1250 mg BID.	The present study will test single doses of PF-06821497 and implement a washout period between doses across treatment periods to minimize exposure of PF-06821497 in the healthy participants. AEs and clinical laboratory results will be monitored on an ongoing basis.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Blood draws for assessment of PK, safety labs, and retained samples.	A blood draw may cause participant discomfort including faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.	Blood draws will be performed by experienced and trained site staff within the confines of the PCRU.
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific assessments according to the SoA.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the bioavailability of a single C mg dose of PF-06821497 CC tablet formulation (Formulation 2) relative to a single C mg dose of PF-06821497 CCI tablet formulation (Formulation 1) under fasted conditions in adult healthy participants	• Plasma AUC_{inf} and C_{max} for PF-06821497. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
Secondary:	**Secondary:**
• To estimate the bioavailability of a single C mg dose of PF-06821497 CC tablet (larger API particle size) formulation (Formulation 3) relative to a single C mg dose of PF-06821497 CC tablet (Formulation 2) and a single C mg dose of the PF-06821497 CCI tablet formulation (Formulation 1) under fasted conditions in adult healthy participants	• Plasma AUC_{inf} and C_{max} for PF-06821497 for CC tablet (larger API particle size) (Formulation 3) relative to CC (Formulation 2) and CCI tablet (Formulation 1) formulations. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
• To estimate the effect of a high-fat, high-calorie meal on the bioavailability of a single CCI mg dose of the PF-06821497 CC tablet formulation (Formulation 2) relative to fasted conditions in adult healthy participants	• Plasma AUC_{inf} and C_{max} for PF-06821497 under fed (high-fat, high-calorie meal) conditions relative to fasting conditions. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
• To estimate the effect of a low-fat, low-calorie meal on the bioavailability of a single CCI mg dose of the PF-06821497 CC tablet formulation (Formulation 2) relative to fasted conditions in adult healthy participants	• Plasma AUC_{inf} and C_{max} for PF-06821497 under fed (low-fat, low-calorie meal) conditions relative to fasting conditions. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
• To evaluate the safety and tolerability of PF-06821497 when administered as a tablet formulation to healthy participants	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, physical examinations, and 12-lead ECGs.
CCI [redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, open-label, 3-period, crossover, single-dose 2-part study in healthyparticipants to investigate the effect of tablet formulation and food on the bioavailability of PF-06821497.

In each part of the study, each enrolled participant will participate in 3 study periods to receive 3 different treatments according to the sequence determined by randomization with 5-day washouts between PF-06821497 administration:

Part 1 (rBA):

- Treatment A – Single CCI mg dose CCI tablet formulation (Formulation 1), under fasting conditions (following an overnight fast of at least 10 hours)
- Treatment B – Single CCI mg dose CCI tablet formulation (Formulation 2), under fasting conditions (following an overnight fast of at least 10 hours)
- Treatment C – Single CCI mg dose CCI tablet formulation (larger API particle size) (Formulation 3), under fasting conditions (following an overnight fast of at least 10 hours)

Part 2 (Food Effect):

- Treatment D – Single CCI mg dose CCI tablet formulation (Formulation 2), under fasting conditions (following an overnight fast of at least 10 hours)
- Treatment E – Single CCI mg dose CCI tablet formulation (Formulation 2), given with a low-fat/low-calorie meal
- Treatment F – Single CCI mg dose CCI tablet formulation (Formulation 2), given with a high-fat/high-calorie meal

Approximately 18 participants will be enrolled to the study intervention. If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective(s), additional participants can be enrolled at the discretion of the investigator upon consulation with the sponsor.

In each part of the study, each enrolled participant will receive 1 of the 3 treatments in each period according to treatment schedule shown in Table 1Table 1. A minimum of C day washout period between successive single doses of PF-06821497 is included to minimize any residual PF-06821497 concentrations prior to start of the next treatment period. For Treatments A, B, and C, following an overnight fast of at least 10 hours, and after the collection of the pre-dose PF-06821497 PK sample on Day 1 of each period, participants will be administered a CCI mg dose of PF-06821497. For Treatment D, following an overnight fast of at least 10 hours, and after the collection of the pre-dose PF-06821497 PK sample on Day 1, participants will be administered a CCI mg dose of PF-06821497. For Treatment E, after an overnight fast of at least 10 hours and after the collection of pre-dose PF-06821497 PK sample on Day 1, participants will receive a low-fat, low-calorie breakfast 30 minutes prior to dosing. For Treatment F, after an overnight fast of at least 10 hours and after the

collection of pre-dose PF-06821497 PK sample on Day 1, participants will receive a high-fat, high-calorie breakfast 30 minutes prior to dosing. Participants are strongly encouraged to consume the breakfast in its entirety. PF-06821497 will be administered as intact tablets with approximately 240 mL of ambient temperature water. Tablets will be swallowed and not chewed. In each period, participants will undergo blood sampling for determination of PF-06821497 PK at timepoints shown in SoA. Participants who withdraw may be replaced at the joint discretion of the investigator and the sponsor.

Table 1. Treatment Schedule

Part 1 (rBA):

Sequence	Period 1	Washout: at least C days between PF-06821497 doses	Period 2	Washout: at least C days between PF-06821497 doses	Period 3
1 (6 Participants)	A		B		C
2 (6 Participants)	B		A		C

Treatment A – CCI formulation (Formulation 1) [redacted] fasted;
Treatment B – CC formulation (Formulation 2) [redacted] fasted;
Treatment C – CC formulation (Formulation 3) [redacted]; larger API particle size) fasted ;

Part 2 (Food effect):

Sequence	Period 1	Washout: at least C days between PF-06821497 doses	Period 2	Washout: at least C days between PF-06821497 doses	Period 3
1 (6 Participants)	D		E		F

Treatment D – CC formulation (Formulation 2) [redacted] fasted;
Treatment E – CC formulation (Formulation 2) [redacted] fed: Low-fat meal;
Treatment F – CC formulation (Formulation 2) [redacted] fed: High-fat meal

In each part, participants will be on the study up to 10 weeks, including the screening and follow-up periods. Participants will be screened within 28 days prior to the first dose of the investigational product in Period 1. Participants will be admitted to the PCRU Day -1 and will be required to remain the PCRU for a minimum of C days until completion of 48 hours PK sampling on Day 3. The investigator could choose to confine participants in the PCRU beyond Day C and discharge them following completion of Day C assessments in Period 3 in each part of the study. Alternatively, participants will be eligible for discharge from the PCRU at C CI hours post dose in each period following review of the discharge safety assessments, provided that the participants are able to return to the PCRU on Day -1 for each of the remaining study periods. If a participant has any clinically significant study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be

asked to remain in the PCRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. A follow-up contact will be completed at least 28 calendar days and up to 35 calendar days after the last administration of PF-06821497 to capture any potential AEs and to confirm appropriate contraception usage. Contact with the participant may be done via a phone call.

4.2. Scientific Rationale for Study Design

The purpose of the study is to investigate the relative bioavailability of tablet formulations of PF-06821497 and to characterize the effect of food on a PF-06821497 CCI tablet formulation. The data generated from this study will be used to support the pivotal study formulation, to inform dose administration instructions for PF-06821497 with regard to dosing with or without food, and to enable the establishment of the API particle size specifications for eventual commercialization.

Relative Bioavailability Assessment: In the ongoing clinical Phase 1 study (C2321001) for evaluating the safety and efficacy of PF-06821497, an CCI tablet formulation of PF-06821497 has been utilized. The current CCI tablet formulation (Formulation 1) has a CCI drug loading with respect to the required pivotal dose and is considered undesirable for further clinical development. A new formulation of PF-06821497 manufactured using a CCI process (Formulation 2) is planned to be used in the pivotal Phase 2/3 trials. Therefore, the primary objective of the rBA study is to compare the relative bioavailability of the CCI tablet formulation (Formulation 2) to that of CCI tablet formulation (Formulation 1) and confirm that they are comparable.

The relative bioavailability of the CCI tablet formulation containing an API with larger particle size (Formulation 3) CCI relative to the WG tablet formulation (Formulation 2) and CCI tablet formulation (Formulation 1), containing API with a standard particle size CCI will be evaluated as a secondary objective of this study. This comparison will enable the establishment of the API particle size specification for the commercial API manufacturing process.

Food effect assessment: Based on the solubility and permeability data collected in the pre-clinical phase, PF-06821497 is considered to be a BCS CCI drug. For this class of compound, food is most likely to show a CCI food effect, due to CCI in fed state. Therefore, PK of the CCI tablet formulation (Formulation 2) following administration of a standard low-fat/low-calorie or high-fat/high-calorie meal will be evaluated as secondary objectives of this study to investigate the effect of food on the bioavailability of PF-06821497. The data from food effect assessment will inform dose administration instructions for PF-06821497 with regard to dosing with or without food and can potentially make future trials easier to conduct given the BID regimen. Given the BID regimen of PF-06821497, evaluating both low and high-fat meal will provide data to guide upcoming studies in terms of flexibility or restriction in administration of IP with different types of meals during the day that may have varying degree of fat content (eg, Breakfast versus dinner).

For the food effect assessment of the study, single doses of CCI mg will be administered with sufficient washout between the doses. The effect of food on PF-06821497 exposures based on its properties (BCS CCI compound, CCI is expected to be less than CCI [2]. Therefore, there is a potential for this study to generate CCI exposures that may be CCI than what was observed in the FIP study. However, the single dose administration at CCI mg is not expected to have significant safety concerns even if there is a CCI in exposure, as PF-06821497 at CCI mg/day CCI has been tolerated following repeated administration with enzalutamide. Further, safety data from at least 3 participants from Part 2 Period 2 (where subjects will receive low-fat meal) will be reviewed before proceeding to Period 3 (high-fat meal condition) to provide an additional safeguard. In addition to the usual participant selection and safety monitoring measures implemented in such healthy volunteer studies, this study restricts the population to participants without a history of liver disease and with normal baseline liver tests, in accordance with FDA guidance provided during the course of the FIH study, in response to one patient developing fatal heptoxicity that has been classified as an important potential but not identified risk for PF-06821497. In addition, post treatment ECG monitoring has been added as additional measure, as one case of G3 QTcF prolongation, potentially related to PF-06821497 has been observed while QTcF prolongation has not been identified as a risk for PF-06821497.

The study is being designed as a crossover study to minimize the potential for intrinsic factors that may impact inter-individual variability in the PK of PF-06821497 from confounding the comparisons of PK parameters across the treatment periods and better estimate the true differences between the study treatments. Between each administered single dose, a C-day washout is proposed to minimize any residual PF-06821497 concentrations prior to start of next period, which is sufficient based on the observed half-life of CCI hours.

4.2.1. Assessment of Safety Data Before Administration of the High-fat Meal in Part 2 of the Study

The high-fat meal is expected to potentially CCI exposures by CCI approximately CCI .[2] In Part 2 of the study, before the Period 3 doses are administered to participants that have eaten a high-fat meal, the safety data for Period 2, including at least 3 participants administered a low-fat meal in Period 2, will be reviewed by the study team and the investigator and assessed based on safety and tolerability. Period 3 will initiate as planned if the doses administered in Period 2 were well-tolerated.

4.2.2. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-06821497 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.3. Collection of Retained Research Samples

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

4.3. Justification for Dose

Part 1: A single CCI mg dose of PF-06821497 is planned for each period in Part 1 (rBA) of this study. A tablet strength of CCI mg is being planned for the pivotal study and hence the rBA assessment in Part 1 of this study is conducted at CCI mg dose which is the single unit CCI dose strength for the tablets being evaluated.

Part 2: A single CCI mg dose of PF-06821497 is planned for each period in Part 2 (food effect) of this study. Based on preliminary data from the ongoing Phase 1 study (C2321001) in advanced cancer patients, PF-06821497 has been well tolerated as monotherapy and in combination with SOC in doses from 75 mg to 1250 mg BID given continuously in 21-day cycles. The highest doses tested in monotherapy and in combination with enzalutamide are 625 mg BID and 1250 mg BID, respectively. No MTD was determined for both the monotherapy and combination arms. Given that PF-06821497 is intended for use in oncology patients, the highest dose or exposure tested in the nonclinical studies does not limit the dose-escalation or highest dose investigated in a clinical trial in cancer patients, which is primarily guided safety findings. As such, the FIP study had evaluated doses beyond the HNSTD dose tested in preclinical toxicology studies, andno major safety concerns have been identified at any of the dose levels. Safety data from ongoing C2321001 study indicate that single doses of PF-06821497 up to CCI mg BID CCI were not associated with any major acute safety concerns.

The effect of food on PF-06821497 exposures based on its properties (BCS CCI compound, CCI is expected to be CCI .[2] Therefore, there is a potential for this study to generate peak exposures that may be CCI than what was observed in the FIP study. However, the single dose administration at CCI mg is not expected to have significant safety concerns even if there is a CCI in exposure, as PF-06821497 at CCI mg/day CCI has been tolerated following repeated administration with enzalutamide. Preliminary analyses of data from C2321001 indicate that there is CCI . In addition, based on preliminary PK data from C2321001 at CCI mg BID dose, the day 1 geometric mean and range of observed unbound C_{max} of PF-06821497 is CCI ng/mL, and CCI ng/mL, respectively. If there is a CCI in peak exposures by food, it would likely result in an unbound C_{max} of approximately CCI ng/mL, which would still be CCI the highest observed C_{max} at CCI mg dose in study C2321001. Considering the healthier population in this study and PCRU confinement where more intense safety monitoring will be conducted, potential risks to study participants can be managed adequately and be mitigated with preventive measures in place that include routine monitoring of adverse events and changes in clinical laboratory test parameters for clinical management, including study drug discontinuation as appropriate to ensure the safety of the study participants. Further, safety data from at least 3 participants from Part 2 Period 2 (where subjects will receive low-fat meal) will be reviewed before proceeding to Period 3 (high-fat meal condition), where maximum food effect is expected, to provide an additional safeguard.

Based on safety data of PF-06821497 as described above, a single CCI mg dose in Part 1 and single CCI mg dose in Part 2 with a washout for 3 periods in this study is expected to pose little risk to healthy adult participants and the potential risks can be managed effectively.

4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants ≥18 years of age, inclusive, at screening.

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

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs and 12-lead ECGs.

Other Inclusion Criteria:

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

4. Evidence of a personally signed and dated ICD indicating that the participant has been informed of all pertinent aspects of the study.

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing) or prior allergic reaction to any component of PF-06821497.

    - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy, prior bariatric surgery, ileal resection, inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease).

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAB or HCVAb. Hepatitis B vaccination is allowed.

    - Chronic liver diseases including alcoholic liver disease, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, human immunodeficiency virus, or other chronic liver disease.

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

3. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

    - Current use or anticipated need for food or drugs that are known strong inducers or inhibitors of CYP3A4/5, including their administration within 10 days or 5 half-lives of the strong inducer or inhibitor of CYP3A4/5, whichever is longer prior to first dose of investigational product. Refer to Section 6.9.

    - Time dependent inhibitors of CYP3A4/5 for atleast 21 days prior to the treatment

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

5. A positive urine drug test.

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

7. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

    - AST or ALT level > ULN;
    - Total bilirubin level >1 × ULN;
    - PT, INR and aPTT outside of normal limits at baseline
    - eGFR <60 mL/min/1.73 m^2 based on the CKD-EPI equation;
    - Absolute neutrophil count <0.8 x LLN.

Other Exclusion Criteria:

9. 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).

10. Use of tobacco or nicotine containing products within 3 months of screening or a positive urine cotinine test (ie, active smokers and those who currently use nicotine containing products are excluded from participation in this study).

11. Pregnant female participants; breastfeeding female participants; fertile male participants and female participants of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 3 months after the last dose of investigational product.

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

13. History of sensitivity to heparin or heparin-induced thrombocytopenia.

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

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their 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 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 2 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample on Day 1 of each Period.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- There will be no predose water restriction for the fed treatment periods in Part 2 of the study (Treatment E and Treatment F) on Day 1. For Treatment E, following an overnight fast of at least 10 hours, participants will start the recommended low-fat (approximately 25% of total caloric content of the meal), low-calorie (approximately 400 to 500 calories) breakfast 30 minutes prior to administration of PF-06821497. Breakfast will be consumed within an approximate 20 minute period with PF-06821497 administered approximately 10 minutes after completion of the meal. Participants are strongly encouraged to consume the low-fat/low-calorie breakfast in its entirety.

- For Treatment F, following an overnight fast of at least 10 hours, participants will start the recommended high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast 30 minutes prior to administration of PF-06821497. Breakfast will be consumed within an approximate 20 minute period with PF-06821497 administered approximately 10 minutes after completion of the meal. Participants are strongly encouraged to consume the high-fat/high-calorie breakfast in its entirety.

- Lunch will be provided approximately 4 hours after PF-06821497 dosing.

- Dinner will be provided approximately 9 to 10 hours after PF-06821497 dosing.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein with the exception for dosing days where a high fat/high calorie or low fat/low calorie meal will be given prior to study intervention. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

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

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

5.3.4. Activity

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

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

- Participants will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the participants exposure to light including high intensity UVB light sources such as tanning beds, tanning booths and sunlamps. Participants should be encouraged to apply sunscreen/sunblock daily.

- Participants will be confined to the procedure room for the first [redacted] hours after dosing on Day 1 of Period 2 and 3 in Part 2 of the study, except to use the bathroom. After this, participants may be ambulatory but should not engage in strenuous activities.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the joint discretion of the investigator and medical monitor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to PF-06821497 tablets.

6.1. Study Intervention(s) Administered

For this study, the study interventions are the tablet formulations of PF-06821497 administered as single dose ([redacted] mg in Part 1, [redacted] mg in Part 2) under fasted or fed conditions; Treatment A [[redacted] mg of [redacted] tablet formulation (Formulation 1), under fasting conditions], Treatment B [[redacted] mg of [redacted] tablet formulation (Formulation 2), under fasting conditions], Treatment C [[redacted] of [redacted] tablet formulation (larger API particle size) (Formulation 3), under fasting conditions], Treatment D [[redacted] mg of [redacted] tablet formulation (Formulation 2), under fasting conditions], Treatment E [redacted] mg of [redacted] tablet formulation (Formulation 2), given with a low-fat/low-calorie meal], Treatment F [[redacted] mg of [redacted] tablet formulation (Formulation 2), given with a high-fat/high-calorie meal]. The PF-06821497 tablet formulations will be supplied by Pfizer.

PF-06821497 [redacted] mg strength tablets for the 3 tablet formulations will be supplied to the PCRU in bulk along with individual dosing containers for unit dosing. A brief description of the PF-06821497 tablet formulations supplied in this study is provided in Table 2.

Table 2. Summary of PF-06821497 Formulations

Description	Material ID (DMID)/ Lot Number	Included in Treatment(s)	Route of Administration
PF-06821497 [redacted] tablets (Formulation 1)	DP-001550/22-DP-00973	Treatment A	Oral
PF-06821497 [redacted] tablets (Formulation 2)	DP-005872/23-DP-01411	Treatment B, D, E and F	Oral
PF-06821497 [redacted] tablets (larger API particle size) (Formulation 3)	DP-005872/23-DP-01412	Treatment C	Oral

6.1.1. Administration

All Treatment Periods:

Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

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

Treatment A [redacted] tablets (Formulation 1) , fasting conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will take a single [redacted] mg dose [redacted] mg tablets) of the

CCI tablet formulation (Formulation 1) of PF-06821497 at approximately 0800 hours (plus or minus 2 hours).

Treatment B [CCI tablets (Formulation 2), fasting conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will take a single CCI mg dose (CCI mg tablets) of the CCI tablet formulation (Formulation 2) of PF-06821497 at approximately 0800 hours (plus or minus 2 hours).

Treatment C CCI tablets (larger API particle size) (Formulation 3), fasting conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will take a single CCI mg dose (CCI mg tablets) of the CCI tablet formulation (larger API particle size) (Formulation 3) of PF-06821497 at approximately 0800 hours (plus or minus 2 hours).

Treatment D [CCI tablets (Formulation 2) , fasting conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will take a single CCI mg dose CCI mg tablets) of the CCI tablet formulation (Formulation 2) of PF-06821497 at approximately 0800 hours (plus or minus 2 hours).

Treatment E [CCI tablets (Formulation 2), fed conditions: low-fat meal]:

Following an overnight fast of at least 10 hours, participants will start the recommended low-fat (approximately 25% of total caloric content of the meal), low-calorie (approximately 400 to 500 calories) breakfast 30 minutes prior to administration of the CCI tablet formulation (Formulation 2) of PF-06821497. Breakfast will be consumed within an approximate 20 minute period with PF-06821497 administered approximately 10 minutes after completion of the meal. Participants are strongly encouraged to consume the low-fat/low-calorie breakfast in its entirety. Percentage of the meal consumed will be documented in the CRF. PF-06821497 should be administered at approximately 0800 hours (plus or minus 2 hours).

Treatment F [CCI tablets (Formulation 2), fed conditions: high-fat meal]:

Following an overnight fast of at least 10 hours, participants will start the recommended high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast 30 minutes prior to administration of the CCI tablet formulation (Formulation 2) of PF-06821497. Breakfast will be consumed within an approximate 20 minute period with PF-06821497 administered approximately 10 minutes after completion of the meal. Participants are strongly encouraged to consume the high-fat/high-calorie breakfast in its entirety. Percentage of the meal consumed will be

documented in the CRF. PF-06821497 should be administered at approximately 0800 hours (plus or minus 2 hours).

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

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

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the PCRU local/site procedures.

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's local/site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

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

PF-06821497 tablets will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

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

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

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

6.6. Dose Modification

No dose modification is anticipated.

6.7. Continued Access to Study Intervention After the End of the Study

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

6.8. Treatment of Overdose

For this study, any dose of PF-06821497 greater than CCI mg in Part 1 and CCI mg in Part 2 within a 24-hour time period ±6 hours will be considered an overdose.

There is no specific treatment for a PF-06821497 overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within C days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

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

As PF-06821497 is primarily metabolized by CYP3A4/5, as determined in in vitro studies, concomitant use of any medications or substances that are strong inducers or inhibitors of CYP3A4/5 are prohibited within 10 days or 5 half-lives, whichever is longer, prior to dosing of study intervention and within 2 days after the last dose of PF-06821497.

Strong CYP3A4/5 inhibitors may include grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan.

Strong CYP3A4/5 inducers may include phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, and St. John's Wort.

Time dependent inhibitors of CYP3A4/5 are prohibited for at least 21 days prior to the treatment. Time dependent inhibitors of CYP3A4/5 may include azamulin, troleandomycin, verapamil, boceprevir, nelfinavir, and telaprevir.

It is preferred that moderate CYP3A4/5 inhibitors and/or inducers be replaced prior to the first dose of study treatment and during study conduct. Moderate CYP3A4/5 inhibitors may include erythromycin, ciprofloxacin, verapamil, diltiazem, atazanavir, fluconazole, darunavir, delavirdine, amprenavir, fosamprenavir, aprepitant, imatinib, tofisopam, and cimetidine. Moderate CYP3A4/5 inducers may include bosentan, efavirenz, etravirine, modafinil, and nafcillin. If the replacement is not possible, then caution should be exercised with coadministration of PF-06821497 with moderate CYP3A4/5 inhibitors and/or inducers.

Additionally, concomitant use of PF-06821497 and a substrate of the CCI renal transporter may increase the exposure of the CCI substrate. Therefore, caution is warranted if coadministration of PF-06821497 with CCI substrates.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

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

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06821497; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- AE requiring discontinuation in investigator's view;
- Positive COVID-19 test.

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

7.1.1. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.
It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Investigator's decision.

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

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact

with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

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

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. In addition, other clinical assessments or specimen collections, eg, retained research samples, may be used without repeat collection, as appropriate.

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 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 they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (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 230 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 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.

8.2. Efficacy Assessments

Not applicable.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

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

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

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

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and 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.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.2. Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes of rest in a supine position by observing and counting the respirations of the participant for 30 seconds and multiplying by 2. When BP is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before BP measurement.

8.3.2.3. Temperature

Temperature will be measured orally. No eating or drinking is allowed for 15 minutes prior to the measurement.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements (from within the current Treatment Period). Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms 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 QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. Clinical Safety Laboratory Assessments

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

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and abnormal during participation in the study or within 48 hours 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 study medical monitor.

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.3.5. COVID-19 Specific Assessments

COVID-19 specific assessments will be performed as per PCRU procedures or by the PI.

8.3.6. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the PF-06821497. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an

ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

8.4.1. 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 undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

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

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

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.4.2. 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.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Appendix 3.

8.4.4. 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 72 hours after last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

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

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure 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 about the occupational exposure 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 must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOP.

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

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

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

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

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

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

8.5. Pharmacokinetics

Blood samples of approximately 2 mL, to provide approximately 0.5 mL plasma, will be collected for measurement of plasma concentrations of PF-06821497 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

Samples will be used to evaluate the PK of PF-06821497. Samples collected for analyses of PF-06821497 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

[redacted]

Samples collected for measurement of plasma concentrations of PF-06821497 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

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.

CCI [redacted]

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

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 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.

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
PK Concentration Population	The PK concentration population is defined as all participants randomized and treated who have at least 1 PF-06821497 concentration in at least 1 treatment period.
PK Parameter Population	The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PF-06821497 PK parameters of primary interest in at least 1 treatment period.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Pharmacokinetic Analysis

9.3.1.1. Derivation of Pharmacokinetic Parameters

Plasma PK parameters of PF-06821497 will be derived (as data permits) from the concentration-time data using standard noncompartmental methods as outlined in Table 3. The PF-06821497 plasma PK parameters will be summarized descriptively by Treatment. Plasma concentrations will be listed and summarized descriptively by Treatment, and nominal PK sampling time. Individual participant and summary profiles (mean and median plots) of the plasma concentration time data will be plotted using actual and nominal times, respectively.

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 time will be used in the derivation of PK parameters.

Table 3. Plasma PF-06821497 PK Parameters Definitions

Parameter	Definition	Method of Determination
AUC_{inf}*	area under the concentration-time curve from time 0 to infinity	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis and k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration	Linear/Log trapezoidal method.
C_{max}	maximum observed concentration	Observed directly from data
CCI	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

9.3.2. Statistical Methods for PK Data

Part 1:

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A (CCI formulation (Formulation 1) CCI mg (CCI) fasted) will be the Reference treatment and Treatment B (CCI formulation (Formulation 2) CCI mg CCI mg) fasted) will be the Test treatment.

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with sequence and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A (CCI formulation (Formulation 1) CCI mg CCI mg) fasted) will be the Reference treatment and Treatment C (CCI formulation (Formulation 3) CCI mg CCI mg; larger API particle size) fasted) will be the Test treatment. For the second comparison, Treatment B (CCI formulation (Formulation 2) CCI mg CCI mg) fasted) will be the Reference treatment and Treatment C (CCI formulation (Formulation 3) CCI mg CCI mg; larger API particle size) fasted) will be the Test treatment.

Part 2:

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effects model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment D (CCI formulation (Formulation 2) CCI mg (CCI mg) fasted) will be the Reference treatment and Treatments E and F (CCI formulation (Formulation 2) CCI mg CCI mg) fed: low-fat meal and CCI formulation (Formulation 2) CCI mg CCI mg) fed: high-fat meal) will be the Test treatments.

9.3.3. Other Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, PR, RR, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, RR and PR abnormalities of potential clinical concern will be described. Safety

data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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

CCI [redacted]

[redacted]

9.4. 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/PD modeling, and/or supporting clinical development.

9.5. Sample Size Determination

Part 1: Sample size of 12 participants will provide adequate precision of 90% CIs. The width of 90% confidence interval for different estimated effects is presented in Table 4.

Table 4. Expected Widths of the 90% CIs for Different Possible Estimated Effects and Parameters of Interest for Part 1 Study

Parameter	Estimated Effect (100*Test/Reference)	90%CI	CI Width
AUC	85%	74.74% to 96.67%	21.94%
	90%	79.13% to 102.36%	23.23%
	95%	83.53% to 108.05%	24.52%
	100%	87.93% to 113.73%	25.81%
	105%	92.32% to 119.42%	27.10%
	110%	96.72% to 125.11%	28.39%
	115%	101.11% to 130.79%	29.68%
C_{max}	85%	68.01% to 106.24%	38.23%
	90%	72.01% to 112.49%	40.48%
	95%	76.01% to 118.74%	42.73%
	100%	80.01% to 124.99%	44.98%
	105%	84.01% to 131.24%	47.23%
	110%	88.01% to 137.49%	49.48%
	115%	92.01% to 143.74%	51.73%

These calculations are based on the estimates of within-subject standard deviations of CCI [redacted] for $\log_e$ AUC_{inf} and $\log_e$ C_{max}, respectively, as obtained from study C2321001.

Part 2: Sample size of 6 participants will provide adequate precision of 90% CIs. The following table presents the width of 90% confidence interval for different estimated effects:

Table 5. Expected Widths of the 90% CIs for Different Possible Estimated Effects and Parameters of Interest for Part 2 Study

Parameter	Estimated Effect (100*Test/Reference)	90%CI	CI Width
AUC	CCI [redacted]	[redacted]	[redacted]
C_{max}	CCI [redacted]	[redacted]	[redacted]

These calculations are based on the estimates of within-subject standard deviations of CCI [redacted] for $\log_e$ AUC_{inf} and $\log_e$ $C_{max,}$, respectively, as obtained from study C2321001.

Participants who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each 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 their 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 their 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 their right to access and correct their personal data and to withdraw consent for the processing of their 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 on which 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 IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 10 days from the previous ICD signature date.

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 will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

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

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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and/or IQMP maintained and utilized by the sponsor or designee.

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

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.

10.1.8. Source Documents

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

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

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

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

The sponsor or designee will perform mornitoring 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 guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor 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 the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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

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

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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 intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and creatinine CystatinC and eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein For suspected DILI[e]: AST/ALT T bili, direct and indirect bili Total bile acids, GGT Total protein, albumin CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative) For suspected DICI/DIKI[f]: Creatinine (Scr) CystatinC (Scys) eGFR (Scr only and combined Scr+Scys) Spot (dipstick) UACR	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[a]	• Urine cotinine • Pregnancy test (β-hCG)[d] • PT, PTT, INR At screening: • FSH[b] • Urine drug screening[c] • Hepatitis B surface antigen • Hepatitis C antibody • Hepatitis B core antibody • HIV

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other

a. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.
e. See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI
f. See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

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.

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

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition 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 or 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 that 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 an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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 During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or 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 or 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: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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 or SAE. The investigator will use clinical judgment to determine the relationship.

- 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.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 theiropinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- 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 DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT. • If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT 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 DCT 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 the 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, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, 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 and Barrier Guidance

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 3 months after the last dose of PF-06821497, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

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

  OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.
- 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

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

- A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; (b) agrees to not donate eggs (ova, oocytes) for the purpose of reproduction 3 months; and (c) at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.3).
  - OR
- Is a WOCBP who agrees to use a highly effective contraceptive method (failure rate of <1% per year) with low user dependency during the intervention period and for at least 3 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The

investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 3 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling a woman with an early, undetected pregnancy.

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

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

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogenonly hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

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

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

    - Oral + barrier*

    - Intravaginal + barrier*

- Transdermal + barrier*

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

   - Oral + barrier*

   - Injectable + barrier*

8. Sexual Abstinence

9. 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.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or 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, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to estimate glomerular filtration rate [Scr-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021;385:1737-49.[3]

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to CTCAE criteria.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs

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

ECG Findings That <u>May</u> Qualify as SAEs

- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS complex>120 ms).
- New-onset right bundle branch block (QRS complex>120 ms).
- 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 (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

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

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

ECG Findings That Qualify as SAEs

- QTcF prolongation >500 ms or > 60 ms from baseline
- 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.

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
%CV	coefficient of variation
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
API	Active Pharmaceutical Ingredients
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval t
AV	atrioventricular
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
b-hCG	b-human chorionic gonadotropin
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
C1D1	Cycle 1 Day 1
C1D15	Cycle 1 Day 15
CCl4	carbon tetrachloride
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{last}	last quantifiable concentration
CCI	[redacted]
CL_p	plasma clearance
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form

Abbreviation	Term
CRO	contract research organization
CRPC	castration resistant prostate cancer
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CTIS	Clinical Trial Information System
CTSUR	Clinical Trial Service Unit Report
CV	cardiovascular
CYP	cytochrome P450
DCT	data collection tool
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DMID	dosage material identification
DSUR	Development Safety Update Report
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
ERCP	Endoscopic retrograde·cholangiao-pancreatography
eSAE	electrionic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clincal Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FIH	first-in-human
FIP	first-in-patient
FL	follicular lymphoma
FSH	follicle-stimulating hormone
F/U	follow-up
f_u	unbound fractions
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GGT	gamma-glutamyl transferase

Abbreviation	Term
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HNSTD	Highest non-severly toxic dose
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IND	Investigational New Drug
INR	international normalized ratio
IP	Investigational Product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IQMP	Integrated quality management plan
IRB	Institutional Review Board
IV	intravenous(ly)
k_{el}	terminal phase rate constant
LBBB	left bundle branch block
LFT	liver function test
LLN	lower limit of normal
Log_e	natural logarithm
MATE	multidrug and toxin extrusion
MATE2K	multidrug and toxin extrusion protein 2
MEC	Minimum effective concentration
MQI	medically qualified individual
CCI	[redacted]
MTD	Maximum therapeutic dose
NA	not applicable
NCA	non-compartmental analysis
OAT	organic anion transporter
OCT	organic cation transporter
PAD	pharmacologic active dose
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
P-gp	p-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PO	Oral
PR	pulse rate

Abbreviation	Term
PRC2	polycomb repressive complex 2
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTT	Partial thromboplastin time
PVC	premature ventricular contraction/complex
QA	Quality assess
QC	Quality control
QD	Once a day
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
rBA	relative Bioavailability
RBC	red blood cell
CCI	[redacted]
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLC	small cell lung cancer
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOC	Standard of care
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
T bili	total bilirubin
TEAE	Treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to reach C_{max}
UACR	urine albumin/creatinine ratio
UGT	Uridine diphosphate glycosyltransferase
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
UVA	ultraviolet A
UVB	ultraviolet B
V_{ss}	volume of distribution at steady-state
CCI	[redacted]
WBC	white blood cell
CCI	[redacted]

Abbreviation	Term
WOCBP	woman/women of childbearing potential
WT	Wild type

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