Title Page

A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE DOSE, 2-SEQUENCE, 3-PERIOD CROSSOVER STUDY TO EVALUATE THE EFFECT OF A LOW-FAT AND HIGH-FAT MEAL ON THE RELATIVE BIOAVAILABILITY OF PF-07284890 IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07284890
Study Intervention Name:	N/A
US IND Number:	CCI
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4471002
Phase:	1

Brief Title: A Phase 1 Study to Evaluate the Effect of a Low-Fat and High-Fat Meal on the Relative Bioavailability of PF-07284890 in Healthy Adult Participants

Document History

Document	Version Date
Original protocol	06 April 2022

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label, Randomized, Single Dose, 2 Sequence, 3 Period Crossover Study to Evaluate the Effect of a Low-fat and High-fat Meal on the Relative Bioavailability of PF-07284890 in Healthy Adult Participants

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Rationale:

The purpose of the study is to evaluate the effect of a low-fat and high-fat meal on the relative bioavailability of PF-07284890 following single dose oral administration of PF-07284890 using 2 of the 100 mg PF-07284890 tablets currently used in the first-in-patient study C4471001 (200 mg per single dose).

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the effect of a low-fat meal on the exposures of PF-07284890 following a single oral 200-mg dose • To evaluate the effect of a high-fat meal on the exposures of PF-07284890 following a single oral 200-mg dose	• Comparison of low-fat meal with fasted PK: The ratio of AUC_{last}, AUC_{inf} (if data permit) and C_{max} of PF-07284890 • Comparison of high-fat meal with fasted PK: The ratio of AUC_{last}, AUC_{inf} (if data permit) and C_{max} of PF-07284890
Secondary:	**Secondary:**
• To characterize the pharmacokinetic parameters of PF-07284890 following a single oral 200-mg dose	• T_{max}, $t_{½}$, CL/F and V_z/F (if data permit).
• To evaluate the safety and tolerability of PF-07284890 in healthy participants	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.

Overall Design:

This is a Phase 1, open-label, randomized, single dose, 3-treatment, 2-sequence, 3-period crossover study to evaluate the effect of a low-fat and high-fat meal on the relative

bioavailability of PF-07284890 following a single oral dose of PF-07284890 using two 100-mg tablets of PF-07284890 in healthy adult participants, males and females of non-childbearing potential. The study will consist of 3 treatments: a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fasted conditions (Treatment A, Reference), a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under low-fat meal fed conditions (Treatment B, Test 1), and a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under high-fat meal fed conditions (Treatment C, Test 2).

Approximately 12 healthy participants will be randomly assigned to study intervention such that approximately 6 participants will be enrolled to each sequence. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the investigator.

Healthy participants will be screened to determine eligibility within 28 days prior to study treatment. Medical history and results of physical examination, physical measurements, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility. Participants will report to the CRU on Day -1, and will be required to stay in the CRU for 15 days and 14 nights.

Eligible participants will be admitted to the CRU at least 12 hours prior to the dosing of PF-07284890 on Day 1 of Period 1. On the morning of Day 1 of each period, participants will receive a single dose of PF-07284890 200 mg as per randomization schedule. Study intervention will be administered with approximately 240 mL of ambient temperature water. In fed periods (Sequence 2 Period 1 and Sequence 1 Period 2 for the low-fat meal and Period 3 for the high-fat meal as shown in Section 1.2), following an overnight fast of at least 10 hours, participants should begin breakfast approximately 30 minutes prior to PF-07284890 administration. For Sequence 2 Period 1 and Sequence 1 Period 2, a low-fat (approximately 25% of total caloric content of the meal), low-calorie (approximately 400 to 500 calories) breakfast will be consumed over approximately a 20-minute interval with PF-07284890 administered within approximately 10 minutes of completion of the meal. For Period 3, a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast will be consumed over approximately a 20-minute interval with PF-07284890 administered within approximately 10 minutes of completion of the meal. Serial PK samples will be collected up to 72 hours post dose. Period 2 will begin on Period 1 Study Day 5 (referred to as Period 2, Day -1). Period 3 will begin on Period 2 Study Day 5 (referred to as Period 3, Day -1). Participants will be discharged from the CRU at the end of Period 3, Study Day 4, following completion of all assessments.

Before the Period 3 doses are administered to participants that have eaten a high-fat meal, the safety data for Periods 1 and 2, including at least 8 participants administered a low-fat meal in Period 1 or 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 Periods 1 and 2 were well-tolerated.

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 CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

A safety follow-up call will be made to participants 28 to 35 days from administration of the final dose of study intervention.

Number of Participants:

Approximately 12 participants will be randomly assigned to study intervention.

Note: "Enrolled" means a participant'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 and ≤65 years of age, inclusive, at the time of signing the ICD.
2. Male participants and female participants of non-childbearing potential 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 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).
4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion Criteria

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

1. Evidence or history of clinically significant uveitis, 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).

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

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

    - Use of PPIs is not allowed within 7 days of study start (C1D1) and during study treatment.

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 (eg, contact with positive case, residence, or travel to an area with high incidence) 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.

4. Current use or anticipated need for drugs that are known strong UGT2B7 inhibitors, including the administration within 10 days or 5 half-lives, whichever is longer, or strong UGT2B7 inducers, including the administration within 5 half-lives plus 10 days, prior to first dose of PF-07284890.

5. Participant who has received a COVID-19 vaccine within 7 days before screening or admission, or who are to be vaccinated with a COVID-19 vaccine at any time during the study confinement period.

6. 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).

7. Positive test result (RT-PCR) for SARS-CoV-2 infection at the time of screening or Day -1.

8. A positive urine drug test at screening or admission.

9. A positive urine cotinine test at screening or admission.

10. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest.

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

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

    - AST **or** ALT level ≥1.25 × ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
    - eGFR <75 mL/min/1.73 m^2 with 10% variation based on the CKD-EPI equation.
    - Hemoglobin < 11 g/dL
    - ANC < 1.5 10e9/L
    - Platelets < 100,000/mm^3

13. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening.

14. Current smokers or history of the use of tobacco- or nicotine-containing products within 6 months of screening.

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

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

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

18. 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 to determine eligibility within 28 days prior to study treatment. Eligible participants will report to the CRU on Day -1, Period 1 and will be required to stay in the CRU for 15 days and 14 nights. A safety follow-up call will be made to participants 28 to 35 days from administration of the final dose of study intervention.

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-07284890 administration:

- Treatment A: Single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fasted conditions (Reference).
- Treatment B: Single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fed conditions, low-fat meal (Test 1).
- Treatment C: Single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fed conditions, high-fat meal (Test 2).

Participants will be randomly assigned to 1 of 2 sequences as shown in Section 1.2.

Statistical Methods:

Pharmacokinetics Analysis

The PK concentration population is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value can be reported.

The PK parameter analysis population is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest can be reported.

PK parameters for PF-07284890 will be analyzed using standard noncompartmental method of analysis. Actual PK sampling times will be used in the derivation of PF-07284890 PK parameters when available, otherwise nominal times will be used. The PF-07284890 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 by treatment using actual and nominal times, respectively.

Natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect 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% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the

ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A (PF-07284890 administered under fasted condition) is the Reference treatment, Treatment B (PF-07284890 administered under fed condition, low-fat meal) is the first Test treatment, Test 1, and Treatment C (PF-07284890 administered under fed condition, high-fat meal) is the second Test treatment, Test 2.

Safety Analysis

All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Ethical Considerations:

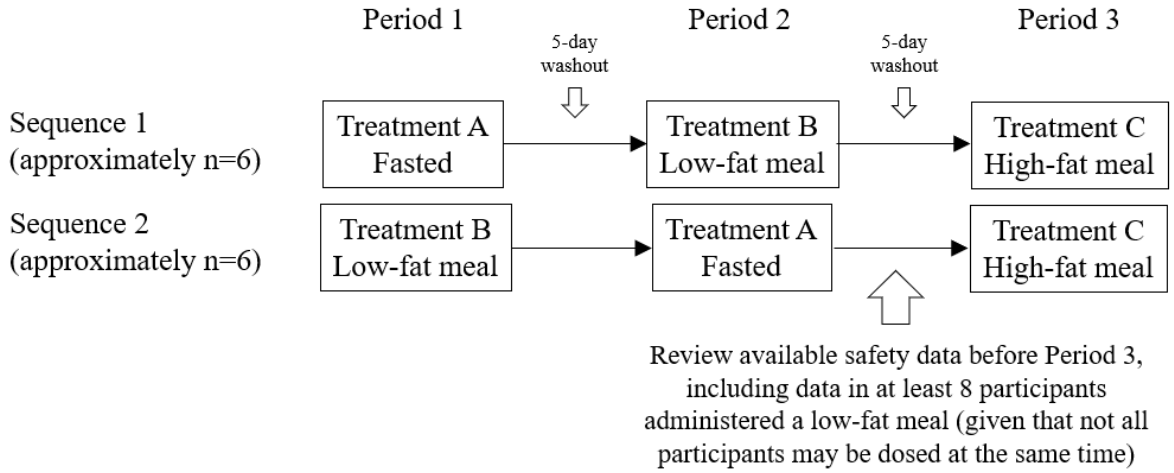
PF-07284890 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate PK, safety and tolerability data for PF-07284890 administered in the fasted and fed state for further clinical development.

- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments.
- Male participants must agree to use appropriate contraception methods.

1.2. Schema

A diagram of the study design is displayed in Figure 1.

Figure 1. C4471002 Study Schema



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 10	**Screening**[a]	**Periods 1-3**[b]																**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**												**Day 2**		**Day 3**	**Day 4**	**28-35 days**[t]	
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	16	24	36	48	72		
Informed consent	X																			
CRU confinement[c]		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		
Inclusion/exclusion criteria	X	X																		
Medical/medication history (update)[d]	X	X																		
Demography[e]	X																			
Physical examination[f]	X	X[f]																		
Safety laboratory (including aPTT, PT-INR and eGFR)[g]	X	X[v]													X					X
FSH[h]	X																			
Urine drug and cotinine testing[i]	X	X																		
HIV, HBsAg, HBcAb, HCVAb	X																			
Contraception check[j]	X	X																	X	X
Single supine 12-lead ECG[k]	X						X			X	X							X		X
Triplicate 12-lead ECG[k]			X[s]																	
Vital signs (BP/PR/temperature)[l]	X		X[s]															X		X
Full ophthalmic exam[m]			If clinically indicated																	
COVID-19 questionnaire[n]	X	X																		

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screening[a]**	**Periods 1-3[b]**																	**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**												**Day 2**		**Day 3**	**Day 4**	**28-35 days[t]**	
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	16	24	36	48	72		
COVID-19 testing[n]	X	X																		
PF-07284890[o]			X																	
PK blood sampling for PF-07284890[p]			X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Retained Research Sample for Genetics (Prep D1)[q]			X																	
CCI [redacted]			[redacted]																	
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Concomitant treatments			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		X
CRU discharge[r]																		X		

a. Screening will be performed within 28 days prior to the first dose of PF-07284890.
b. Period 2 will begin on Study Period 1, Day 5 (referred to as Period 2, Day -1). Period 3 will begin on Study Period 2, Day 5 (referred to as Period 3, Day -1). Day -1 activities will be performed only for Day -1 of Period 1 unless otherwise indicated.
c. Participants will be admitted to the CRU at least 12 hours prior to PF-07284890 dose on Day 1 of Period 1. Participants will be discharged on Day 4 of Study Period 3 following completion of all assessments.
d. Medical history will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days. Medical history will be recorded at screening and updated on Day -1 of Period 1.
e. Demographics will include participant race, ethnicity, age, and gender during the screening visit.
f. Physical examination will be performed by trained medical personnel at the investigator site at screening or Day -1 of Period 1 only (height and weight must be obtained at screening to obtain BMI for eligibility criteria). A brief PE will be performed on Day -1 of Periods 2 and 3, and may be performed at other designated time points at the discretion of the investigator.
g. Safety laboratory assessments including urinalysis, hematology, chemistry and coagulation will be performed at the indicated time-points, including Day -1 and Day 2 at 24 hours post-dose of all 3 Periods. 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.
h. For postmenopausal (amenorrheic for at least 12 consecutive months) female participants only.
i. Urine drug and cotinine (mandatory) and alcohol breath test (at discretion of the investigator) will be performed at screening from Days -28 to -2 and again on Day -1 of Period 1. These tests may be performed at any other time at the discretion of the investigator.
j. The investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly according to contraception guidelines.
k. 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. Day 4 ECGs are for Period 3 only. Single ECGs are needed for screening, times after the study intervention has been administered, Day 4 of Period 3, and upon early termination/discontinuation, while triplicate ECGs are needed for baseline.

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screening**[a]	**Periods 1-3**[b]																**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**												**Day 2**		**Day 3**	**Day 4**	**28-35 days**[t]	
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	16	24	36	48	72		

l. Single supine BP and PR will be performed following at least a 5-minute rest in a supine position. BP and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. Day 4 measurements are for Period 3 only. Temperature will be measured as per CRU standard practice. RR will be collected if the PR is outside of normal range.
m. Full ophthalmic exam will be conducted if treatment emergent ocular AEs are observed.
n. See Section 8.3.6 for details.
o. PF-07284890 will be administered orally on Day 1 after overnight fasting until the start of study procedures for each treatment period. PF-07284890 will be administered orally and in fasted or fed state according to the conditions described in Protocol Section 5.3.2 Meals and Dietary Restrictions.
p. One (approximately 3 mL) blood sample for PK analysis of PF-07284890 will be taken at the designated time points post dose in each treatment period.
q. Retained Research Samples Prep D1 for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. These samples will be collected during Period 1 only.
r. Participants will be discharged on Day 4 of of Period 3 after completion of all assessment.
s. Collect at pre-dose for all 3 periods. For fed periods (Sequence 2 Period 1 and Sequence 1 Period 2 for the low-fat meal and Period 3 for the high-fat meal), the ECGs should be done before the pre-dose PK sample, and both should be done before the meals.
t. Contact may occur via telephone and must occur 28 to 35 days from administration of the final dose of study intervention.
CCI [redacted]
v. Safety laboratories will be done on Day -1 of all 3 periods.

2. INTRODUCTION

PF-07284890 (also known as ARRY-461) is a potent, selective, highly brain-penetrant small-molecule inhibitor of BRAF V600 mutations that is currently being developed for the treatment of BRAF V600-mutant solid tumors with or without brain involvement.

2.1. Study Rationale

The purpose of the study is to evaluate the effect of a low-fat and high-fat meal on the relative bioavailability of PF-07284890 following single dose oral administration of PF-07284890 using 2 of the 100 mg PF-07284890 tablets currently used in the first-in-patient study C4471001 (200 mg per single dose). Results from the study will be used to inform food instructions for patients in PF-07284890 first-in-patient study C4471001, Phase 1b.

2.2. Background

BRAF V600 mutations occur in approximately 50% of melanoma and PTC, 45% of ATC, 15% of CRC, 2% of NSCLC and less commonly in several other tumor types (based on data from SEER database, seer.cancer.gov). BRAF mutations drive constitutive MAPK pathway activation and in turn proliferation with enhanced cellular survival. Small molecule BRAF inhibitors block mutant BRAF, MAPK signaling, proliferation and survival in some BRAF V600-mutant tumor cells, effects that are enhanced by combination with MEK inhibitors. To date, there are 3 BRAF inhibitor/MEK inhibitor combinations approved for select BRAF V600-mutant cancers: dabrafenib/trametinib (melanoma, NSCLC and ATC), vemurafenib/cobimetinib (melanoma) and encorafenib/binimetinib (melanoma).

Metastatic spread to the CNS is a particularly poor prognostic factor for many solid cancers, with average survival typically <6 months.[1] Among solid tumors, metastatic melanoma and NSCLC have the highest risks of spread to the CNS, with lifetime prevalences of 40-60% and 20-40%, respectively.[2,3,4]

Due to poor brain penetration and limited intracranial activity in early clinical trials, randomized studies of approved BRAF/MEK inhibitors in patients with melanoma and NSCLC (the frequency of brain metastases in CRC and ATC is low) excluded patients with untreated (ie, with local brain therapy), symptomatic (including a requirement for steroids and anti-epileptic therapy to control symptoms) and/or progressing brain metastases.[5,6,7] Recent studies of BRAF/MEK inhibitor combination therapy in patients with solid tumor malignancies with brain metastases therapies have yielded intracranial response rates of between 41-75% in asymptomatic patients and 44-59% in symptomatic patients, with duration of response ranging from a median 12 months in patients with treated brain metastases to 4.5 months in patients with symptomatic brain metastases. [5,6,8,9] The addition of immunotherapy to these combinations yielded response rates of 54 and 59% (including 29% intracranial CR), with median intracranial and overall DoR not reached (12 month landmark global PFS was 56.6%).[10] Patients with BRAF V600-mutant melanoma and NSCLC with metastases to the brain, therefore, usually receive local brain therapy (eg, SRS, surgical resection, WBRT) at some point during their disease course. SRS and surgery are generally limited to 3 or fewer lesions (SRS) or a single large (>3 cm) or posterior fossa lesion (surgery) and do not control disease at untreated sites. WBRT causes accelerated cognitive

decline and was no better than supportive care in NSCLC patients.[11] There is therefore an unmet need to identify new treatment approaches that target BRAF V600-mutant cancers both systemically and in the brain.

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-07284890 can be found in the current IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

After oral administration, plasma exposures of PF-07284890 (AUC and C_{max}) increased with dose in all species and the absolute oral bioavailability was moderate to complete. GLP TK studies in the rat (doses of 10, 30 and 60 mg/kg) and monkey (doses of 10, 30 and 100 mg/kg) showed less than dose-proportional exposures, as might be expected based on relatively low aqueous solubility (ie, in simulated gastric fluid at 37ºC at a pH of 1.2, 131.6 µg/mL, and in fasted state simulated intestinal fluid at a pH of 6.5, 7.6 µg/mL).

In vitro and in vivo metabolite identification suggested that PF-07284890 was metabolized through multiple oxidative and/or glucuronosyltransferase enzymes. Comparisons of across species suggested that direct N-glucuronidation is predicted to be the predominant metabolic route in humans. PF-07284890 glucuronidation is the primary route of metabolism in human hepatocytes with minor contribution from CYP3A4 and aldehyde oxidase. An in vitro study conducted to characterize the involvement of 11 selected human UGTs isoforms in the metabolism of PF-07284890 indicated that UGT2B7 was the principal human isoform likely responsible for primary glucuronide conjugates. Renal clearance was a minor elimination route of unchanged PF-07284890 in rats (<1% of an IV dose) and is predicted to be a minor route across all species, including humans.

Additional information of the nonclinical PK and metabolism of PF-07321332 is available in the current IB.

2.2.3. Nonclinical Safety

Safety pharmacology studies were conducted in rats and monkeys to assess the effects of PF-07284890 on key organ systems (cardiovascular, respiratory, neurobehavioral and gastrointestinal function). Rats and monkeys received single oral doses of up to 100 mg/kg PF-07284890. There were no significant in vivo safety pharmacology findings seen in either species. Additionally, PF-07284890 was evaluated at concentrations up to 100 µM in the in vitro GLP hERG channel assay and showed an IC_{50} of 70.15 µM.

The toxicological evaluation of PF-07284890 included: 28-day repeat-dose studies in Sprague Dawley rats and cynomolgus monkeys, a genotoxicity assay (Ames), a local tolerance study (GI irritation in the rat) and an in vitro phototoxicity study. All of these studies were conducted in accordance with international regulatory guidelines for nonclinical toxicity studies and in adherence to current GLP guidelines.

Following 28 days of once-daily oral administration of PF-07284890 (10, 30 or 60 mg/kg) to Sprague Dawley rats, the toxicological response was characterized primarily by the clinical

observations of hindlimb swelling, requiring euthanasia of 6 (out of 150) rats, and mild clinical pathology changes (decreased ALP, decreased red cell parameters, increased reticulocytes, increased white cell parameters, increased aPTT and increased urine volumes); all of which resolved in the recovery animals. It is important to note that many of the PF-07284890 -treated animals were observed to have blistering, swelling and scab/crust formation on the hindlimbs, however, in all but the 6 animals that were euthanized the findings resolved or were of reduced severity and incidence with continued dosing.

Target organs in the study were testes, epididymides, heart, and skin. Organ weight decreases in epididymides at 60 mg/kg, increases in heart at 30 and/or 60 mg/kg dose in females, and increases in liver, ovaries, and spleen in males and/or females were noted at all dose levels. Myxomatous degeneration of the heart valves at 30 and 60 mg/kg and degeneration of seminiferous tubules in the testes and debris in the lumen and decreased cellularity of sperm in the epididymides at 30 and 60 mg/kg were considered adverse histopathology changes from terminal necropsy. All PF-07284890 -related changes from terminal necropsy exhibited significant recovery, except for those in the testes and epididymides at 30 and 60 mg/kg.

Based on the requirement for euthanasia, due to the impairment of mobility and pain (due to paw/hind limb swelling) at the lower dose level, the NOAEL could not be determined. However, these skin effects were not seen in rats until Study Day 10 and a single female required euthanasia due to this effect. The STD_{10} of 60 mg/kg was determined from test article-related lethality or irreversible and life-threatening findings. The lowest dose of 10 mg/kg corresponded to plasma AUC_{24hr} on Study Day 1 of 192 and 517 µg•hr/mL in male and female rats respectively, 12-32 multiple over the planned clinical dose (Table 1) based on comparison to the geometric mean AUC_{24hr} for a 200-mg single dose (ie, based on C1D1) as shown in Table 4.

Table 1. MOEs for Nonclinical Species Compared to Humans at Dose Levels of Interest[a]

Subject area	Key Findings	Margin for HV C1D1 (AUC)	Margin for HV C1D1 (C_{max})
General Tox Rat 28-Day Study QD oral 10, 30, 60 m/k/d (473.05)	Beginning on Study Day 10 skin effects with rash and/or paw and hindlimb swelling all doses (10 mg/kg margin shown)	Male = 12x Female = 32x	Male = 13x Female = 21x
	Myxomatous degeneration of heart valves, degeneration of seminiferous tubules of testes with decreased sperm in the epididymis at >30 mg/kg	30 mg/kg M = 39x 30 mg/kg F = 74x	30 mg/kg M = 35x 30 mg/kg F = 55x
	NOAEL not achieved due to impairment of mobility from hind limb swelling and pain requiring euthanasia at 10 mg/kg (a single female rat) (10 mg/kg MOE shown)	Male = 12x Female = 32x	Male = 13x Female = 21x

Table 1. MOEs for Nonclinical Species Compared to Humans at Dose Levels of Interest[a]

Subject area	Key Findings	Margin for HV C1D1 (AUC)	Margin for HV C1D1 (C_{max})
	STD_{10} 60 mg/kg based on 4/32 early terminated animals	Male = 59x Female = 110x	Male = 41x Female = 67x
General Tox NHP 28-Day Study QD oral 10, 30, 100 m/k/d (473.04)	Well tolerated for 28 days		
	Minimal stomach ulceration 100 mg/kg	5x	8x
	NOAEL and HNSTD 100 mg/kg	5x	8x

a. Exposures from nonclinical TK data were divided by human monotherapy geometric mean AUC_{24hr} and C_{max} values as appropriate at the 200 mg dose level (data shown in Table 4).

Following 28 days of once-daily oral administration of PF-07284890 (10, 30 or 100 mg/kg) in cynomolgus monkeys, no adverse toxicological findings were observed, and the only histopathologic finding was minimal stomach ulceration at the high dose corresponding to a plasma AUC_{24} of 84.4 µg•hr/mL. Given the lack of adverse findings at any dose level, the NOAEL and HNSTD for daily oral dosing of PF-07284890 in male and female cynomolgus monkeys for 28 days was 100 mg/kg.

In addition to the nonclinical investigations summarized above, there was no evidence of genotoxicity from the bacterial reverse mutation assay and no adverse effects on GI mucosa in the rat GI irritation assay.

PF-07284890 was determined to have phototoxic potential in the in vitro neutral red uptake assay.

2.2.4. Clinical Overview

PF-07284890 is being evaluated as a single-agent and in combination with binimetinib in Study C4471001.

2.2.4.1. First-in-Human Study (C4471001)

Study C4471001 is an ongoing Phase 1a/b, open-label, multicenter study of the safety, PK and preliminary clinical activity of PF-07284890 in adult participants with selected BRAF V600-mutant advanced or metastatic solid tumor malignancies and primary brain tumors. The study is being conducted in 2 parts, Phase 1a (Dose Escalation) and Phase 1b (Dose Expansion and a DDI sub-study). The Phase 1a dose escalation will evaluate the safety and PK of monotherapy (PF-07284890 alone) and combination therapy (PF-07284890 plus binimetinib) repeat-dosing. Phase 1b dose expansion will evaluate efficacy, safety, and PK at the MTD/RDE of the combination therapy (PF-07284890 plus binimetinib) in 5 cohorts of patients and a DDI Sub-Study.

CCI [redacted]

2.2.4.1.1. Study Design

Phase 1a – Dose Escalation

The study plans to enroll approximately 35 adult participants with selected BRAF V600-mutant advanced or metastatic solid tumor malignancies and primary brain tumors to determine the MTD and/or recommended dose for further study of PF-07284890 alone and in combination with binimetinib 45 mg BID. As of 10 January 2022, 4 dose levels (50 mg QD, 100 mg QD, 200 mg QD, 200 mg BID) of PF-07284890 monotherapy had been evaluated and 3 dose levels of PF-07284890 had been evaluated (100 mg QD, 100 mg BID, and 150 mg BID) in combination with binimetinib 45 mg BID. Patients included in the dose escalation are required to have evidence of disease progression despite prior treatment. Patients enrolled into the dose escalation are not required to have brain involvement, but the trial initially restricted enrollment to patients with brain lesions ≤ 4 cm and whose brain involvement was asymptomatic for at least 14 days prior to the start of study treatment. Once concentrations of PF-07284890 at steady state met or exceeded 0.168 µg/mL in at least two-thirds of participants at the same dose level, a level at which antitumor activity in the brain and systemically was expected, patients whose brain involvement was symptomatic or whose brain lesions exceeded 4 cm were allowed to enroll. Additionally, once doses considered therapeutic were to be tested, patients with BRAF V600mutant melanoma, NSCLC, CRC or ATC who had not received prior BRAFi were allowed to enroll. Patients are required to have ECOG PS 0 or 1, adequate hematologic, renal, and liver function, must have resolution to prior adverse effects from prior treatments, and must not require immediate local intervention for the treatment of brain metastases/primary brain tumor.

Phase 1b – Dose Expansion

After identification of the combination MTD/recommended dose for further study, approximately 40 participants will be enrolled to each of Cohorts 1-4 and 20 participants to Cohort 5 of Phase 1b dose expansion based on tumor type, symptomatic versus asymptomatic brain involvement, and prior treatment history.

2.2.4.1.2. Clinical Safety of PF-07284890

As of 10 January 2022, the study has dosed 22 patients in the Phase 1a Dose Escalation.

Monotherapy:

At the 4 monotherapy dose levels assessed (50 mg QD, 100 mg QD, 200 mg QD, and 200 mg BID), 12 patients have been treated, 9 patients were DLT evaluable, and no patients experienced DLTs (Table 2). Based on the safety of the prior dose and the available PK data for PF-07284890 suggesting that twice daily dosing would be needed to achieve trough concentrations at the fu-adj IC_{90}, the recommendation to alter the schedule to twice daily dosing was supported by the BLRM and adopted with the next dose level studied being 200 mg BID.

Preliminary safety results of the 200 mg QD dose of PF-07284890 in patients resulted in treatment emergent adverse events of Grade 2 worsening gout related to underlying condition

(not related to PF-07284890) and sinus infection/sinusitis (not related to PF-07284890) as well as Grade 1 anorexia, arthritis, back pain, nausea and pain, all in 1 patient each. With repeat dosing of the 200 mg BID dose schedule, one patient experienced Grade 3 pneumonia, considered not related to study drug. Grade 2 events, occurring in 1 patient each, were ejection fracture decreased considered related to the patient's underlying disease, fatigue, and oxygen saturation decreased preceding diagnosis of pneumonia, as well as maculo-papular rash. Dizziness, dry skin, and benign skin lesion were reported in 1 patient each as Grade 1. At lower doses, the only severe events reported were fatal disease progression of cancer, suprapubic pain related to the patient's underlying disease, and 2 patients with Grade 3 anemia, considered unrelated to study treatment in 1 case, and in another patient with Grade 1 anemia at baseline in the setting of renal dysfunction and iron deficiency. Data from repeat-dosing in patients suggests that the 200 mg dose is well tolerated.

Table 2. PF-07284890 Monotherapy Dose Level Review and Status

PF-07284890 Dose	DLRM Summary and Decision
50 mg QD	Number of participants reviewed: 2 Number of DLTs observed: 0 Escalate to 100 mg QD
100 mg QD	Number of participants reviewed: 4, 2 DLT evaluable Number of DLTs observed: 0 Escalate to 200 mg QD
200 mg QD	Number of participants reviewed: 3 Number of DLTs observed: 0 Escalate to 200 mg BID
200 mg BID	Number of participants reviewed: 3, 2 DLT evaluable Number of DLTs observed: 0 Escalate to 300 mg BID

DLT evaluable: In the absence of a dose-limiting toxicity (DLT) a participant must receive ≥ 75% of their planned dose during the DLT observation period, which is the first cycle of treatment, a 21-day cycle.

Combination:

Within the combination therapy dose escalation, 3 dose levels of PF-07284890 have been studied in combination with binimetinib 45 mg BID, 10 patients have been treated and 9 were DLT evaluable. At the first dose level (PF-07284890 100 mg QD + binimetinib 45 mg BID), one patient of 4 evaluable experienced DLTs of Grade 3 creatine phosphokinase increased and Grade 3 hypertension, considered related to binimetinib. Based on the safety of the prior dose and the available PK data for PF-07284890 suggesting that twice daily dosing would be needed to achieve trough concentrations at the fu-adj IC_{90}, the recommendation to alter the schedule to twice daily dosing was supported by the BLRM and adopted with the next dose level studied being 100 mg BID. No DLTs were observed at the 100 mg BID or 150 mg BID levels (Table 3).

Table 3. PF-07284890 Combination with Binimetinib (45 mg BID) Dose Level Review and Status

PF-07284890 Dose	DLRM Summary and Decision
100 mg QD	Number of participants reviewed: 4 Number of DLTs observed: 1 Escalate to 100 mg BID
100 mg BID	Number of participants reviewed: 4, 3 DLT evaluable Number of DLTs observed: 0 Escalate to 150 mg BID
150 mg BID	Number of participants reviewed: 2 Number of DLTs observed: 0 Escalate to 225 mg BID

DLT evaluable: In the absence of a dose-limiting toxicity (DLT) a participant must receive ≥ 75% of their planned dose during the DLT observation period, which is the first cycle of treatment, a 21-day cycle.

2.2.4.2. Summary of PF-07284890 Pharmacokinetics in Human

Single and repeat dose PK data from study C4471001 for monotherapy (Table 4) and for combination therapy when coadministered with binimetinib (Table 5) have been obtained under fasted conditions. PF-07284890 plasma exposure increased in a less than dose proportional manner. For monotherapy, the geometric mean dose-normalized AUC_{24hr} for the 200 mg QD dose was approximately 1.83- and 1.43-fold higher than for the 50-mg dose on C1D1 and C1D15, respectively, when a 4-fold increase would be expected for linear PK. The T_{max} ranged from 1.5 to 6.0 hours across dose groups. The median $t_{½}$ across dose groups ranged from 5.7 to 10 hours. PF-07284890 exposures were somewhat higher for combination therapy than for monotherapy, with the difference attributable to PK variability.

The accumulation ratio based on AUC values, R_{AUC}, for patients administered PF-07284890 QD ranged from 0.709 to 1.31, suggesting limited accumulation for QD administration. For BID administration, the limited available data indicate more accumulation occurs, with an R_{AUC} value of 1.69 for the 100 mg BID combination therapy cohort.

Table 4. PF-07284890 Plasma PK Parameters Observed During Monotherapy Dose Escalation in C4471001[a]

PF-07284890 Dose and Regimen	Cycle and Day (N)	C_{max}, ng/mL	T_{max}, hr	AUC_{τ}, ng hr/mL	C_{trough}, ng/mL[b]	$t_{½}$, hr	R_{Cmax}	R_{AUC}
50 mg QD	C1D1 (2)	795	1.5	8850	–	6.17[c]	–	–
	C1D15 (2)	1440	1.5	11500	166	10.0	1.79	1.31
100 mg QD	C1D1 (4)	1610 (40.3)	5.0	14400 (40.5)	–	5.83	–	–
	C1D15 (3)	1090 (16.2)	4.0	10400 (8.34)	115 (71.7)	9.11	0.703 (37.1)	0.709 (45.2)

Table 4. PF-07284890 Plasma PK Parameters Observed During Monotherapy Dose Escalation in C4471001[a]

PF-07284890 Dose and Regimen	Cycle and Day (N)	C_{max}, ng/mL	T_{max}, hr	AUC_{τ}, ng hr/mL	C_{trough}, ng/mL[b]	$t_{½}$, hr	R_{Cmax}	R_{AUC}
200 mg QD	C1D1 (3)	1580 (20.3)	6.0	16200 (22.5)	–	5.68	–	–
	C1D15 (3)	1820 (15.5)	2.0	16500 (8.12)	116 (329)	9.64	1.15 (36.6)	1.02 (14.3)
200 mg BID	C1D1 (3)	1890 (39.2)	6.0	17000[d]	–	–	–	–
	C1D15	ND	ND	ND	ND	ND	ND	ND

a. Analysis includes bioanalytical data available through 21DEC2021, and results are preliminary data that did not use the actual sample times. Values are Geometric mean (geometric %CV) except for when N <3, for which median values are presented, and for T_{max} and $t_{½}$, where median is presented. ND = no data.
b. C_{trough} is the Cp value pre-dose on C1D15.
c. Only could be determined for 1 subject.
d. Only could be determined for 2 subjects.

Table 5. PF-07284890 Plasma PK Parameters Observed During Combination Dose Escalation in C4471001[a]

PF-07284890 Dose and Regimen (N)	Cycle and Day (N)	C_{max}, ng/mL	T_{max}, hr	AUC_{τ}, ng hr/mL	C_{trough}, ng/mL[b]	$t_{½}$, hr	R_{Cmax}	R_{AUC}
100 mg QD	C1D1 (4)	1700 (59.0)	3.5	18000 (94.7)	–	10.3[c]	–	–
	C1D15 (3)	1710 (77.2)	4.0	14700 (38.6)[c]	166 (53.8)	7.09	1.16 (119)	1.09 (73.9)
100 mg BID	C1D1 (4)	1810 (62.7)	4.0	11100 (72.8)[c]	–	–	–	–
	C1D15 (4)	2170 (34.4)	2.0	16400 (42.0)	761 (67.2)	–	1.20 (55.1)	1.69 (31.0)[c]
150 mg BID	C1D1 (2)	2790	4.0	18900	–	–	–	–
	C1D15 (0)	ND	ND	ND	ND	ND	ND	ND

a. Analysis includes bioanalytical data available through 21DEC2021, and results are preliminary data that did not use the actual sample times. Values are Geometric mean (geometric %CV) except for when N <3, for which median values are presented, and for T_{max} and $t_{½}$, where median is presented. ND = no data.
b. C_{trough} is the Cp value pre-dose on C1D15.
c. Only could be determined for 3 subjects.

2.3. Benefit/Risk Assessment

PF-07284890 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and PK data for PF-07284890 administered in the fasted and fed state for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07284890 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-07284890		
Potential risks associated with PF-07284890 include the following: GI irritation, skin toxicity, phototoxicity, heart valve ultrastructural changes, hyperplasia of several tissues including the GI tract, increased urine volume, decreased testicular size and oligospermia, mild decrease in red blood cell count, mild increase in white blood cell count, increased heart rate and vascular inflammation. Potential risks associated with other approved BRAF inhibitors include the following: feeling tired, eye effects (including pain, redness, light sensitivity and/or vision loss), rash, nausea that could lead to vomiting, painful joints, new or growing cancers on the skin and in the body, birth deformities or fetal death from effects on a developing fetus (only observed in animals to date), changes in how electrical impulses are conducted in the heart which may increase the risk of an irregular heartbeat, bleeding including in the gastrointestinal tract, skin reaction which could be severe, liver toxicity, cardiomyopathy.	The potential risks are based on nonclinical toxicology studies in the rat and monkey. GI irritation (minimal stomach ulcerations) occurred in the 28-day monkey study and it was reversible. Structural changes in the heart valves (resulting in thickening of the valve leaflets) was seen in the 28-day rat study with near complete resolution after a non-dosing recovery period. Skin toxicity (swelling, blisters, scabs) was seen in rat hind paws and was reversible. Adverse effects on male rat reproductive organs (testicular atrophy/degeneration and hypospermia) of up to marked severity were seen and these were not completely reversible after a 28-day non-dosing recovery period. Also, in the rat only: minimal to mild decreases in RBC, Hgb and Hct; minimal increases in WBC, neutrophils and eosinophils and mild increases in aPTT were observed and were reversible. Preliminary safety data from the ongoing clinical trial show a majority of adverse events observed with monotherapy administration are low grade and consistent with the adverse event profile of BRAF inhibitors in a BRAF mutant advanced cancer population. Preliminary safety results of the 200 mg QD continuous dosing of PF-07284890 in patients resulted in treatment emergent adverse events of Grade 2 worsening gout related to underlying condition and sinus infection/sinusitis as well as Grade 1 anorexia, arthritis, back pain, nausea and pain, all in 1 patient each. AEs observed were similar to common AEs observed in an advanced cancer population.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5). AEs and clinical laboratory results will be monitored on an ongoing basis. A complete blood count will be performed to monitor for any changes in hematology parameters (eg, RBC, Hgb, Hct, WBC, neutrophils, eosinophils). Coagulation testing will be performed to monitor for any changes in aPTT. Physical exams will be performed to assess overall status including skin checks to monitor for AEs of the skin. Ophthalmic exam if ocular AEs are observed. ECGs will be performed to monitor for changes in cardiac rhythms. Maintaining sufficient margins of exposure between the rat and human (ie, ≥35-fold, see Table 1) is thought to mitigate risk associated with the heart and testicular findings.

2.3.2. Benefit Assessment

PF-07284890 will not provide any clinical benefit to healthy participants in this study. Any anticipated benefit to participants would be in terms of contribution to the process of developing a new therapy in an area of unmet medical need.

2.3.3. Overall Benefit/Risk Conclusion

PF-07284890 is not expected to provide any clinical benefit to healthy participants in this study. Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with PF-07284890 are justified by the anticipated benefits, in terms of contribution to the process of developing a new therapy in an area of unmet medical need.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the effect of a low-fat meal on the exposures of PF-07284890 following a single oral 200-mg dose • To evaluate the effect of a high-fat meal on the exposures of PF-07284890 following a single oral 200-mg dose	• Comparison of low-fat meal with fasted PK: The ratio of AUC_{last}, AUC_{inf} (if data permit) and C_{max} of PF-07284890 • Comparison of high-fat meal with fasted PK: The ratio of AUC_{last}, AUC_{inf} (if data permit) and C_{max} of PF-07284890
Secondary:	**Secondary:**
• To characterize the pharmacokinetic parameters of PF-07284890 following a single oral 200-mg dose	• T_{max}, $t_{½}$, CL/F and V_z/F (if data permit).
• To evaluate the safety and tolerability of PF-07284890 in healthy participants	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.
CCI [redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, randomized, single dose, 3-treatment, 2-sequence, 3-period crossover study to evaluate the effect of a low-fat and high-fat meal on the relative bioavailability of PF-07284890 following a single oral dose of PF-07284890 using two 100-mg tablets of PF-07284890 in healthy adult participants, males and females of non-childbearing potential. The study will consist of 3 treatments: a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fasted conditions (Treatment A, Reference), a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under low-fat meal fed conditions (Treatment B, Test 1), and a single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under high-fat meal fed conditions (Treatment C, Test 2). There will be a total of 2 treatment sequences shown in Section 1.2 with the assigned Treatments A, B or C in each treatment period.

Approximately 12 healthy participants will be randomly assigned to study intervention such that approximately 6 participants will be enrolled to each sequence. Participants who discontinue from the study for non-safety reasons may be replaced at the sponsor's discretion in collaboration with the investigator.

Healthy participants will be screened to determine eligibility within 28 days prior to study treatment. Medical history and results of physical examination, physical measurements, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility.

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-07284890 administration:

- Treatment A: Single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fasted conditions (Reference).
- Treatment B: Single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fed conditions, low-fat meal (Test 1).
- Treatment C: Single oral dose of 200 mg PF-07284890 (2 × 100 mg tablets) under fed conditions, high-fat meal (Test 2).

Participants will be randomly assigned to 1 of 2 sequences as shown in Section 1.2. Serial PK samples will be collected at timepoints shown in the SoA.

The total planned duration of participation, from the screening visit to the last Follow-up phone call, is up to approximately 11 weeks. Participants will be screened within 28 days prior to the first dose of investigational products and if all eligibility criteria are fulfilled, the participants will report to the CRU on Day -1 of Period 1 and will be required to stay in the CRU for 15 days and 14 nights.

Eligible participants will be admitted to the CRU at least 12 hours prior to the dosing of PF-07284890 on Day 1. On the morning of Day 1 of each period, participants will receive a single dose of 200 mg PF-07284890 as per randomization schedule. Study intervention will be administered with approximately 240 mL of ambient temperature water. In the fasted period (Sequence 1 Period 1 and Sequence 2 Period 2), participants will get their first dose after an overnight fast of at least 10 hours. In fed periods (Sequence 2 Period 1 and Sequence 1 Period 2 for the low-fat meal and Period 3 for the high-fat meal as shown in Section 1.2), following an overnight fast of at least 10 hours, participants should begin breakfast approximately 30 minutes prior to PF-07284890 administration. For Sequence 2 Period 1 and Sequence 1 Period 2, a low-fat (approximately 25% of total caloric content of the meal), low-calorie (approximately 400 to 500 calories) breakfast will be consumed over approximately a 20-minute interval with PF-07284890 administered within approximately 10 minutes of completion of the meal. For Period 3, a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast will be consumed over approximately a 20-minute interval with PF-07284890 administered within

approximately 10 minutes of completion of the meal. Serial PK samples will be collected up to 72 hours post dose for all periods. Period 2 will begin on Study Period 1, Day 5 (referred to as Period 2, Day -1). Period 3 will begin on Study Period 2, Day 5 (referred to as Period 3, Day -1). Participants will be discharged from the CRU at the end of Period 3, Study Day 4, following completion of all assessments.

After participants have been confined in the CRU, they will be discharged at the discretion of the investigator. 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 CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow up. A safety follow-up call will be made to participants 28 to 35 days from administration of the final dose of study intervention.

4.2. Scientific Rationale for Study Design

The objective of the study is to evaluate the effect of a low-fat or high-fat meal on the relative bioavailability of PF-07284890 following single 200-mg dose oral administration using a 100 mg tablet formulation of PF-07284890 in healthy adult participants. A crossover design is used to control variability between participants and account for any period effects.Between each administered single dose, a 5-day washout is proposed to minimize any residual PF-07284890 concentrations prior to start of the next period, which is sufficient based on the observed half-life of approximately 5.7 to 10 hours (Table 4).

4.2.1. Assessment of Safety Data Before Administration of the High-fat Meal

The high-fat meal is expected to potentially increase exposures by up to approximately 2-fold.[12] Before the Period 3 doses are administered to participants that have eaten a high-fat meal, the safety data for Periods 1 and 2, including at least 8 participants (given that participants may not all be dosed at the same time) administered a low-fat meal in Period 1 or 2 and at least data from Day 1 through Day 3 of Period 2, will be reviewed by the study team and the investigator and assessed based on safety and tolerability. Period 3 will take place after a discussion between the study team and the investigator. Period 3 will initiate as planned if the doses administered in Periods 1 and 2 were well-tolerated.

Severe nonserious AEs considered as related to study intervention in 2 participants in a period would require a dose reduction. Any SAE considered related to study intervention would require a dose reduction. Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug related by the PI and sponsor. If the SAE is determined to be either drug related or unknown and is ≥ severe or CTCAE Grade 3, dosing of participants will be stopped. If the SAE is determined to be either drug related or unknown and is <severe or CTCAE Grade 3, the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be

implemented. Such a plan could include reducing the dose or adding appropriate safety monitoring.

4.2.2. Choice of Contraception/Barrier Requirements

Nonclinical studies suggest risk for severe manifestations of developmental toxicity at relevant clinical exposures for PF-07284890. 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.

[redacted]

4.3. Justification for Dose

A single 200 mg dose of PF-07284890 is planned for each period of this study.

Following 28 days of once-daily oral administration of PF-07284890 (10, 30 or 60 mg/kg) to Sprague Dawley rats (the sensitive species) in a GLP toxicology study, the STD_{10} was 60 mg/kg. For the lowest dose of 10 mg/kg, exposures in male and female rats, respectively, are estimated to be 12-32 multiple over those of the planned clinical dose (ie, see details in Section 2.2.3). The effect of food on PF-07284890 exposures based on its properties (Biopharmaceutics Classification System Class II compound, weak base) is expected to be less than a 2-fold increase;[12] a 2-fold increase in human exposures would reduce these margins to be ~6-16 multiple over those of the planned clinical dose. The clinical data from C4471001 are also important for justifying the 200 mg dose.

Clinical experience with PF-07284890 is based on the FIH study, C4471001, in which dose-finding is being conducted based on the safety and PK of repeat doses of PF-07284890. As of 10 January 2022, the study has dosed 22 patients in the Phase 1a Dose Escalation. At the 4 monotherapy dose levels assessed (50 mg QD, 100 mg QD, 200 mg QD, and 200 mg BID), 12 patients have been treated, 9 patients were DLT evaluable, and no patients experienced DLTs (Table 2).

Preliminary safety results of the 200 mg QD dose of PF-07284890 in patients resulted in treatment emergent adverse events of Grade 2 worsening gout related to underlying condition and sinus infection/sinusitis as well as Grade 1 anorexia, arthritis, back pain, nausea and pain, all in 1 patient each. With repeat dosing of the 200 mg BID dose schedule, one patient experienced Grade 3 pneumonia, considered not related to study drug. Grade 2 events, occurring in 1 patient each, were ejection fracture decreased considered related to the patient's underlying disease, fatigue, and oxygen saturation decreased preceding diagnosis of

pneumonia, as well as maculo-papular rash. Dizziness, dry skin, and benign skin lesion were reported in 1 patient each as Grade 1. At lower doses, the only severe events reported were fatal disease progression of cancer, suprapubic pain related to the patient's underlying disease, and 2 patients with Grade 3 anemia, considered unrelated to study treatment in 1 case, and in another patient with Grade 1 anemia at baseline in the setting of renal dysfunction and iron deficiency. Data from repeat-dosing in patients suggests that the 200 mg dose is well tolerated.

Based on clinical PK data, the AUC_{24hr} from the highest tolerated dose of 200 mg BID is estimated to be approximately 3.4-fold higher than the AUC_{24hr} for a single dose of 200 mg (ie, based on the accumulation ratio of 1.69 observed for 100 mg BID administration, Table 5, compared to a single dose, BID administration can be expected to have approximately 2 x 1.69-fold higher AUC_{24hr}). Food may increase the AUC_{24hr}, but this 3.4-fold margin based on fasted-state PK increases confidence in the safety of the single daily dose given one time every 5 days for 3 doses. The 5-day interval between doses is expected to avoid any accumulation.

A single dose of 200 mg PF-07284890 given once every 5 days for 3 doses is considered safe to be used in healthy volunteers.

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 and ≤65 years of age, inclusive, at the time of signing the ICD.

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

2. Male participants and female participants of non-childbearing potential (Section 10.4.2) 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 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

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

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence or history of clinically significant uveitis, 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).

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

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

   - Use of PPIs is not allowed within 7 days of study start (C1D1) and during study treatment.

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 (eg, contact with positive case, residence, or travel to an area with high incidence) 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).

4. Current use or anticipated need for drugs that are known strong UGT2B7 inhibitors, including the administration within 10 days or 5 half-lives, whichever is longer, or strong UGT2B7 inducers, including the administration within 5 half-lives plus 10 days, prior to first dose of PF-07284890. Refer to Section 6.9 Prior and Concomitant Therapy and Appendix 9.

5. Participant who have received a COVID-19 vaccine within 7 days before screening or admission, or who are to be vaccinated with a COVID-19 vaccine at any time during the study confinement period.

Prior/Concurrent Clinical Study Experience:

6. 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:

7. Positive test result (RT-PCR) for SARS-CoV-2 infection at the time of screening or Day -1.

8. A positive urine drug test at screening or admission.

9. A positive urine cotinine test at screening or admission.

10. 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.

11. 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.

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

    - AST **or** ALT level ≥1.25 × ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
    - eGFR <75 mL/min/1.73 m^2 based on the CKD-EPI equation.
    - Hemoglobin <11 g/dL
    - ANC <1.5 × 10^9/L
    - Platelets <100,000/mm^3

Other Exclusion Criteria:

13. 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).

14. Current smokers or history of the use of tobacco- or nicotine-containing products within 6 months of screening.

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

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

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

18. 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 at least 1 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. All 3 periods will have a 10-hour fast, followed by pre-dose ECGs and PK sampling (which will be followed by food in the fed periods, Sequence 2 Period 1 and Sequence 1 Period 2 for the low-fat meal and Period 3 for the high-fat meal, prior to dosing).

- For the fasted period (Sequence 1 Period 1 and Sequence 2 Period 2), water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks may be consumed with meals and the evening snack.

- For the first fed period, low-fat meal (Sequence 2 Period 1 and Sequence 1 Period 2 for the low-fat meal) only, a low-fat (approximately 25% of total caloric content of the meal), low-calorie (approximately 400 to 500 calories) meal will be used for the evaluation of a food effect in this study. The provided meal will be similar in composition to the meal referenced in the FDA guidance on food-effect bioavailability and fed bioequivalence studies.[15] On Day 1 of the first fed period,

following an overnight fast of at least 10 hours, participants should begin breakfast approximately 30 minutes prior to PF-07284890 administration. The breakfast will be consumed over approximately a 20-minute interval with PF-07284890 administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to complete the entire breakfast. There are no water restrictions prior to and after dosing.

- For the second fed period, high-fat meal (Period 3) only, a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) meal will be used for the evaluation of a food effect in this study. The provided meal will be similar in composition to the meal referenced in the FDA guidance on food-effect bioavailability and fed bioequivalence studies.[15] On Day 1 of the fed Period 3, following an overnight fast of at least 10 hours, participants should begin breakfast approximately 30 minutes prior to PF-07284890 administration. The breakfast will be consumed over approximately a 20-minute interval with PF-07284890 administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to complete the entire breakfast. There are no water restrictions prior to and after dosing.

- Lunch will be provided approximately 4 to 5 hours after dosing.

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

- An evening snack may be permitted.

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

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 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.

- Participants will not have used tobacco- or nicotine-containing products for 6 months prior to screening and will not use such products during the screening period or after confinement in the CRU.

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 confined to the procedure room for the first 4 hours after dosing on Day 1, except to use the bathroom. After this, participants may be ambulatory but should not engage in strenuous activities.

5.3.5. Photosensitivity

Given the potential for phototoxicity from nonclinical toxicology studies with PF-07284890, 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 sunlight, and high intensity UVB light sources such as tanning beds, tanning booths and sunlamps. Participants should be encouraged to apply sunscreen/sunblock daily and to wear clothing that covers areas of exposed skin when outdoors during daylight hours until discharge from the CRU, which is more than 5 half-lives from the last dose of PF-07284890.

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.

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-07284890.

6.1. Study Intervention(s) Administered

Study Intervention(s)	
Intervention Name	PF-07284890
Type	Drug
Dose Formulation	Tablet

Study Intervention(s)	
Unit Dose Strength(s)	100 mg
Dosage Level(s)	3 single 200-mg doses
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Open-label study intervention will be provided in bulk (high-density polyethylene bottle) labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	PF-07284890 ARRY-461 AR00504461

PF-07284890 will be provided by Pfizer as 100 mg tablets for oral administration at the CRU.

Tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

Investigational product will be administered orally and according to the conditions described in the SoA section and Protocol Section 5.3.2 Meals and Dietary Restrictions.

For **fasted** period (Sequence 1 Period 1 and Sequence 2 Period 2):

- On Day 1, following an overnight fast of at least 10 hours, the participants will receive 200 mg PF-07284890 (as 2 × 100 mg tablets) administered orally at approximately 08:00 hours (plus or minus 2 hours) without breakfast/standard meal on Day 1.

For **fed** periods (Sequence 2 Period 1 and Sequence 1 Period 2 for the low-fat meal and Period 3 for the high-fat meal):

- On Day 1, following an overnight fast of at least 10 hours, participants will receive breakfast approximately 30 minutes prior to dosing which is to be completed within approximately 20 minutes as outlined in Section 5.3.2 Meals and Dietary Restrictions. The participants will then receive 200 mg PF-07284890 (as 2 × 100 mg tablets) administered orally at approximately 08:00 hours (plus or minus 2 hours).

For **all** 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 all tablet formulations 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.

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 intervention 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 IPM or PCRU site procedures.

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

6. Study intervention should be stored in its original container.

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 intervention will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study intervention are provided in the IPM and PCRU's site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in

compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

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 or participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-07284890 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. See the IPM and/or CRU's site procedures for instructions on how to prepare the study intervention for administration.

6.3. Assignment to Study Intervention

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

6.4. 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. A 200-mg dose is the maximum dose that will be administered. In case a dose reduction is necessary, the study intervention dose will be reduced or the study will be stopped early.

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-07284890 greater than the prescribed regimen within a 24-hour time period ±6 hours will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

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

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate for at least 5 half-lives or 28 calendar days (whichever is longer) after the overdose of PF-07284890.
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 7 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).

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

6.9. Prior and Concomitant Therapy

Participants will abstain from all concomitant treatments, except for the treatment of adverse events. 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.

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.

The following sections contain information on the DDI properties of PF-07284890 and concomitant medications that are prohibited or must be used with caution. These DDI properties are needed for when concomitant medicines must be used to treat AEs. A list of example prohibited medications (eg, strong CYP3A inhibitors and inducers) is provided in Section 10.9, Appendix 9: Prohibited Concomitant Medications That May Result in DDI.

CCI [redacted]

[redacted]

CYP3A4/5:

Concomitant use of PF-07284890 and a CYP3A4/5 substrate may increase or decrease the exposure of the CYP3A4/5 substrate. Coadministration of PF-07284890 with CYP3A4/5 substrates with narrow therapeutic indices, such as astemizole, terfenadine, cisapride, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil and fentanyl (excluding transdermal patch), or ergot alkaloids (ergotamine, dihydroergotamine)[16,17] is not permitted. Coadministration with other CYP3A4/5 substrates is permitted but caution is warranted.

CYP2B6:

Concomitant use of PF-07284890 and a CYP2B6 substrate may decrease the exposure of the CYP2B6 substrate. PF-07284890 coadministration with CYP2B6 substrates (eg, a sensitive substrate like bupropion and narrow therapeutic index substrates like efavirenz, also a sensitive substrate, and cyclophosphamide) [16,17] is permitted but caution is warranted.

CYP2C9:

Concomitant use of PF-07284890 and a CYP2C9 substrate may increase the exposure of the CYP2C9 substrate. CYP2C9 substrates of a narrow therapeutic index, may include warfarin,

phenytoin, glimepiride, glipizide, glyburide, ibuprofen, diclofenac, indomethacin, naproxen, rosiglitazone, sulfamethoxazole, tolbutamide, candesartan, irbesartan, losartan and valsartan.[16,18] PF-07284890 coadministration with these and other CYP2C9 substrates is permitted but caution is warranted.

BCRP:

Concomitant use of PF-07284890 and a BCRP inhibitor or inducer may alter the rate and/or extent of PF-07284890 absorption, which could potentially increase (inhibitor) or decrease (inducer) PF-07284890 exposures. PF-07284890 coadministration with BCRP inhibitors or inducers is permitted but caution is warranted.

P-glycoprotein:

Concomitant use of PF-07284890 and a P-glycoprotein substrate may increase the exposure of the P-glycoprotein substrate. PF-07284890 coadministration with P-glycoprotein substrates is permitted but caution is warranted.

Acid Reducing Agents:

Concomitant use of PF-07284890 and an acid reducing agent (eg, PPIs) may cause reduced exposures to PF-07284890. PPIs are not allowed within 7 days of study start (C1D1) and during study treatment, but other acid reducing agents (eg, H2 blockers, antacids) may be used, but only between 2 and 3 hours after administration of each dose of PF-07284890.

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07284890; 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 study intervention.

7.1.1. ECG Changes

A participant who meets either bulleted criterion based on ECG readings will be withdrawn from the study intervention.

- QTcF >500 ms.
- Change from baseline: QTcF >60 ms and QTcF >450 ms.

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

7.1.2. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants in a given period are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.3. 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.

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.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that 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 210 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, skin, 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 and PR 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. BP and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time.

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. If the pulse rate is outside of the normal limits, respiratory rate will also be collected.

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

RR will be collected if the PR is outside of normal range. 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.

8.3.2.3. Temperature

Temperature will be measured orally. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement. Temperature will be measured as per CRU standard practice.

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.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected before dose administration on Day 1 of each period and before the meal for Sequence 1 Period 2, Sequence 2 Period 1, and Period 3 will serve as each participant's baseline QTcF value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any 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 a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) 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. Ophthalmic Examinations

Full ophthalmic examination will be performed by an ophthalmologist if treatment emergent ocular AEs are observed (SoA) including best corrected visual acuity, slit lamp examination, and intraocular pressure.

For participants with clinical suspicion of retinal abnormalities occurring during study conduct (ie, photopsia, metamorphopsia, impairment of visual acuity) or RVO, additional assessments of OCT, dilated fundoscopy, optical coherence tomography (for RPED), and fluorescein angiography of the central 30 degrees (for RVO) should be conducted if deemed clinically necessary.

8.3.5. 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.

Urine drug and cotinine (mandatory) and alcohol breath test (at discretion of investigator) will be performed at screening from Days -28 to -2 and again on Day -1. These tests may be performed at any other time at the discretion of the investigator.

8.3.6. COVID-19 Specific Assessments

Participants will be checked for exposure to positive participant, residence or travel in area of high incidence and COVID-19 related signs and symptoms. Participants will be tested for COVID-19 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19-like symptoms. Additional testing may be required by local regulations and guidance or by the PI.

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 they consider 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 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'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 50 hours after the last dose.

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

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal

demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion 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 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 Sections 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

8.5.1. Plasma for Analysis of PF-07284890

Blood samples of approximately 3 mL, to provide a minimum of 1.2 mL plasma, will be collected for measurement of plasma concentrations of PF-07284890 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of PF-07284890. Samples collected for analyses of plasma PF-07284890 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-07284890 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.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

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8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.7.1. Specified Gene Expression (RNA) Research

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

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

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

No statistical hypothesis will be tested in 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 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.
Safety analysis set	All participants 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.
PK Concentration Population	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value can be reported.
PK Parameter Analysis Population	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest can be reported.

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. Primary Endpoint(s) Analysis

9.3.1.1. Definition of Endpoint(s)

Plasma PK parameters of PF-07284890 will be derived (as data permit) from the concentration-time data using standard noncompartmental methods of analysis as outlined in Table 6. Actual PK sampling times will be used in the derivation of PF-07284890 PK parameters when available. 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 6. Plasma PF-07284890 PK Parameters Definitions

Parameter	Definition	Method of Determination
AUC_{inf}*	Area under the plasma concentration-time curve from time zero extrapolated 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
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time to reach C_{max}	Observed directly from data as time of first occurrence
$t_{½}$*	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve. Only those data points judged to describe the terminal loglinear decline will be used in the regression.
CL/F*	Apparent clearance	$Dose/AUC_{inf}$
V_z/F*	Apparent volume of distribution for extravascular dosing	$Dose/(AUC_{inf} \bullet k_{el})$

*If data permit.

9.3.1.2. Statistical Methods for Pharmacokinetic Data

Using data from Periods 1 and 2, natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect 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% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A (PF-07284890 under fasted condition) is the Reference treatment and Treatment B (PF-07284890 administered under fed condition, low-fat meal) is the Test treatment.

Using data from Treatments A and C, natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with treatment and sequence as a fixed effect and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A (PF-07284890 under fasted condition) is the Reference treatment and Treatment C (PF-07284890 administered under fed condition, high-fat meal) is the Test treatment.

The plasma concentrations of PF-07284890 will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

The PK parameters listed in Table 6 will be summarized descriptively by treatment.

Additional specifications about the tables, listings, and figures will be outlined in the SAP.

9.3.2. Other Safety Analyses

All safety analyses will be performed on the safety analysis set.

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

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.

9.3.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

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

Safety QTcF Assessment

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

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. Changes from baseline will be defined as the change between the postdose QTcF value and the predose single ECG value on Day 1.

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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

A sample size of 12 evaluable participants will provide 90% confidence intervals (CIs) for the difference between treatments of ±0.2995 and ±0.3337 on the natural log scale for AUC_{inf} and C_{max}, respectively, with 80% coverage probability. Table 7 presents the width of 90% CI for different estimated effects.

Table 7. Confidence Interval Estimation of PK Endpoints

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf}	150%	1.1118, 2.0237	0.9119
	170%	1.2600, 2.2936	1.0335
	180%	1.3342, 2.4285	1.0943
	190%	1.4083, 2.5634	1.1551
	200%	1.4824, 2.6983	1.2159
	210%	1.5565, 2.8332	1.2767
	220%	1.6306, 2.9682	1.3375
	230%	1.7048, 3.1031	1.3983
	250%	1.8530, 3.3729	1.5199
C_{max}	150%	1.0744, 2.0942	1.0198
	170%	1.2176, 2.3734	1.1558
	180%	1.2893, 2.5131	1.2238
	190%	1.3609, 2.6527	1.2918

Table 7. Confidence Interval Estimation of PK Endpoints

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
	200%	1.4325, 2.7923	1.3598
	210%	1.5041, 2.9319	1.4278
	220%	1.5758, 3.0715	1.4957
	230%	1.6474, 3.2111	1.5637
	250%	1.7906, 3.4904	1.6997

These calculations are based on estimates of within-participant standard deviation of 0.3491 and 0.3890 for $\log_e AUC_{tau}$ and $\log_e C_{max}$ respectively, based on the results from Study C4471001.

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. 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.

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

10.1.3. Data Protection

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

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

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

10.1.4. Committees Structure

This study will not use an E-DMC.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the 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.

10.1.6. Data Quality Assurance

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

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.

10.1.7. Source Documents

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

Data reported on the CRF or entered in the 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 the 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 monitoring 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.

10.1.8. 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 IRB/ECs, 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.

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. 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 and (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 8. 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)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[a]	aPTT, PT-INR, eGFR (CKD-EPI) Urine drug screening[c] Urine cotinine test At screening only: • FSH[b] • Hepatitis B surface antigen • Hepatitis C antibody • Hepatitis B core antibody • HIV

a. Only if UTI is suspected and urine dipstick is positive (1+) for blood, protein, nitrites or leukocyte esterase.
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).

The table below is a list of reflex safety laboratory tests, which are required for certain circumstances only. This is not an exhaustive list; other special reflex tests may be added as needed.

Table 9. Protocol-Required Follow-Up Safety Laboratory Assessments (In Case of Abnormality)

Hematology	Chemistry	Urinalysis on Site	Other
If Hb/RBC abnormal: MCV, MCH, MCHC Neutrophils (%) Eosinophils (%) Basophils (%) Lymphocytes (%) Monocytes (%) RBC morphology RBC distribution width	**Required:** For suspected DILI: 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: Creatinine (Scr) CystatinC (Scys) eGFR (Scr only and combined Scr+Scys) Spot (dipstick) UACR	**Local Laboratory** Microscopy and culture for positive local dipstick tests[a]	• Hepatitis B DNA • Hepatitis C RNA

a. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both. Any positive results are to be reported as an AE.

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

CCI

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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated information will be recorded in the originally 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 28 days after the last dose of study intervention, 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.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 2 (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 is not a WOCBP (see definition in Section 10.4.3) and is not breastfeeding.

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:

<u>Highly Effective Methods That Have Low User Dependency</u>

1. Implantable progestogen-only 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;
    - Intravaginal;
    - Transdermal.

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

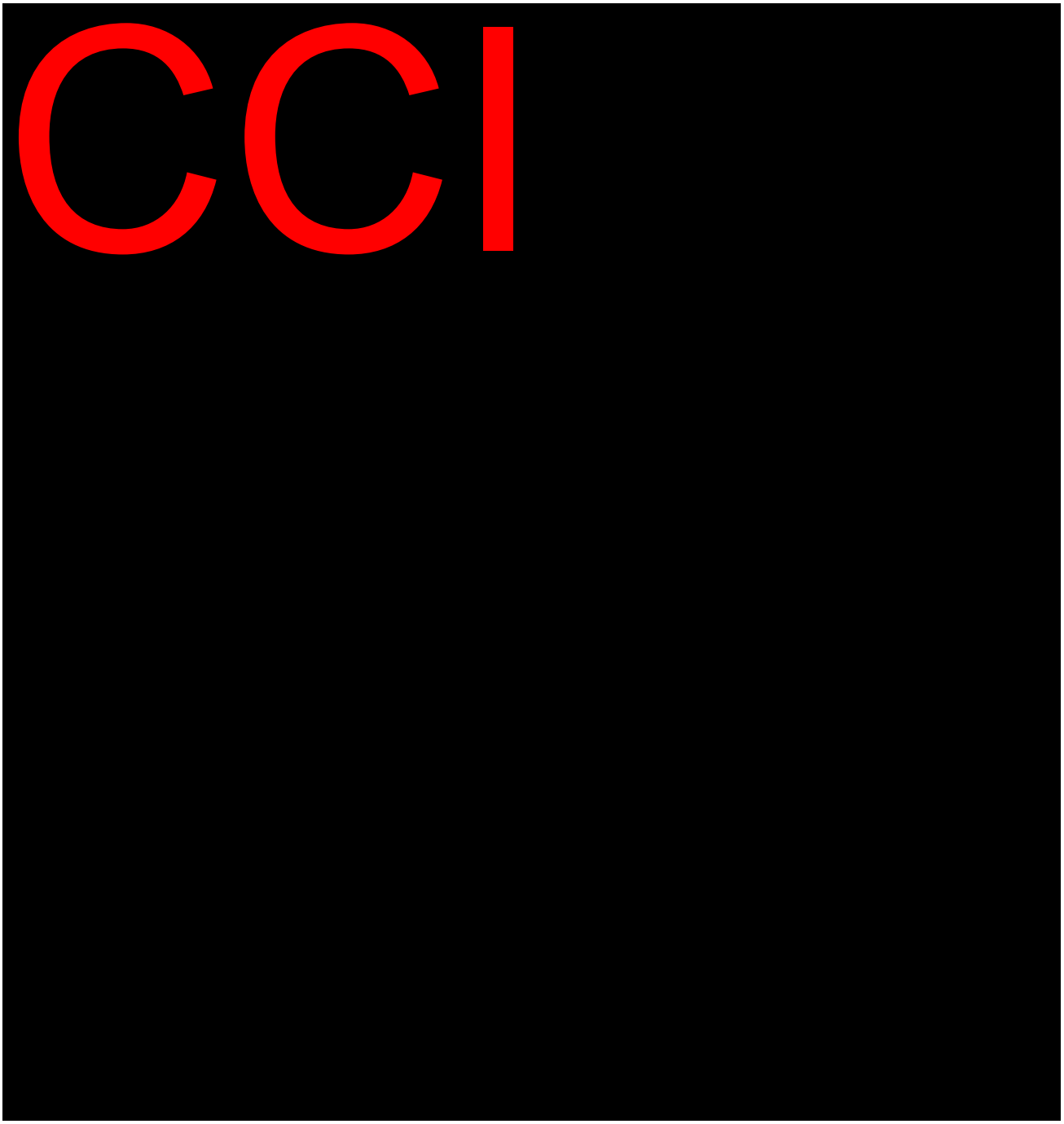
    - Oral;
    - Injectable.

Sexual Abstinence

8. 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.

Other Effective Methods

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
10. Male or female condom, with or without spermicide.
11. Cervical cap, diaphragm, or sponge with spermicide.
12. 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.

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

- QTcF prolongation >500 ms.
- 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

- 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: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with PF-07284890 throughout the conduct of the study, and some have required washout period as listed in the table.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

Table 10. Prohibited Concomitant Medications that May Result in DDI

Drug Category	Drugs	Guidance	Required Washout Period Prior to the First Dose of PF-07284890
[redacted]			
Proton pump inhibitors	dexlansoprazole esomeprazole ilaprazole [a] lansoprazole omeprazole pantoprazole rabeprazole	Prohibited	7 days
PF-07799933 as Perpetrator of DDI			
CYP3A substrates that have a narrow therapeutic index (NTI)	alfentanil amiodarone argatroban astemizole [a] carbamazepine cisapride [a] cyclosporine dihydroergotamine	Prohibited	N/A

Table 10. Prohibited Concomitant Medications that May Result in DDI

Drug Category	Drugs	Guidance	Required Washout Period Prior to the First Dose of PF-07284890
	ergotamine fentanyl (excluding transdermal patch) pimozide quinidine sirolimus tacrolimus terfenadine		

a. Not approved in the US as of October 2020, but may be available in other countries including Korea, China and Mexico.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
%CV	percent coefficient of variation
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	aanaplastic thyroid cancer
AUC	area under the plasma concentration-time curve
AUC_{24hr}	area under the plasma concentration-time curve from time zero to 24 hours
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (Clast).
AUC_{tau}	area under the plasma concentration-time curve from time zero to tau (ie, over the dosing interval)
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BID	twice daily
BLRM	Bayesian Logistic Regression Model
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BRAF	B-type Raf proto-oncogene
BRAFi	B-type Raf proto-oncogene inhibitor
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
C1D15	Cycle 1 Day 15
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

Abbreviation	Term
CL/F	apparent clearance
C_{last}	the last quantifiable concentration
C_{max}	maximum observed concentration
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
Cp	plasma concentration
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CTMS	Clinical Trial Management System
C_{trough}	pre-dose plasma concentration
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DME	drug metabolizing enzyme
DNA	deoxyribonucleic acid
DoR	duration of response
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
ECOG	Eastern Cooperative Oncology Group
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
eSAE	electrionic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clincal Trials (European Clinical Trials Database)
FIH	first in human

Abbreviation	Term
FSH	follicle-stimulating hormone
HR	heart rate
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCVAb	hepatitis C antibody
hERG	human ether-à-go-go-related gene
Hgb	hemoglobin
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	heart rate
HRT	hormone replacement therapy
HV	healthy volunteer
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
IC_{90}	90% of the maximum inhibition concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IQMP	Integrated Quality Management Plan
IRB	Institutional Review Board
IV	intravenous(ly)
K_2-EDTA	dipotassium ethylenediaminetetraacetic acid
K_{el}	terminal phase rate constant
LBBB	left bundle branch block
LFT	liver function test
MAPK	mitogen-activated protein kinase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MEK	mitogen/extracellular signal regulated kinase
NHP	nonhuman primate
MOE	margin of exposure

Abbreviation	Term
MQI	medically qualified individual
MTD	maximum tolerated dose
N/A	not applicable
ND	no data
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
NTI	narrow therapeutic index
OCT	optical coherence tomography
PCR	polymerase chain reaction
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PE	physical examination
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PR	pulse rate
PS	performance status
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTC	papillary thyroid cancer
PVC	premature ventricular contraction/complex
QD	once daily
QRS	time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
R_{AUC}	accumulation ratio based on AUC
RBC	red blood cell
R_{Cmax}	accumulation ratio based on C_{max}
RDE	recommended dose for expansion
RNA	ribonucleic acid
RPED	retinal pigment epithelial detachment
RR	respiratory rate
RT-PCR	reverse transcriptase-polymerase chain reaction
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
Scys	serum cystatin C

Abbreviation	Term
SEER	Surveillance, Epidemiology, and End Results
SoA	schedule of activities
SOP	standard operating procedure
SRS	stereotactic radiosurgery
SRSD	Single Reference Safety Document
STD_{10}	severely toxic dose in 10% of the animals
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal elimination half-life
T bili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TK	toxicokinetics
T_{max}	time to reach C_{max}
UACR	urine albumin/creatinine ratio
CCI	[redacted]
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
UVB	ultraviolet B
V_z/F	apparent volume of distribution for extravascular dosing
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WBRT	whole-brain radiotherapy

11. REFERENCES

1. Stelzer KJ. Epidemiology and prognosis of brain metastases. Surg Neurol Int 2013;4(Suppl 4):S192-202.

2. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004;22(14):2865-72.

3. Cohen JV, Tawbi H, Margolin KA, et al. Melanoma central nervous system metastases: current approaches, challenges, and opportunities. Pigment Cell Melanoma Res 2016;29(6):627-42.

4. Mujoomdar A, Austin JH, Malhotra R, et al. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. Radiology 2007;242(3):882-8.

5. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with $BRAF^{V600}$-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol 2017;18(7):863-73.

6. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17(9):1248-60.

7. Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018;19(10):1315-27.

8. McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. Ann Oncol 2017;28(3):634-41.

9. Holbrook K, Lutzky J, Davies MA, et al. Intracranial antitumor activity with encorafenib plus binimetinib in patients with melanoma brain metastases: a case series. Cancer 2020;126(3):523-30.

10. Menter T, Tzankov A. Genetic alterations of 9p24 in lymphomas and their impact for cancer (immuno-)therapy. Virchows Arch 2019;474(4):497-509.

11. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet 2016;388(10055):2004-14.

12. Owens K, Argon S, Yu J, et al. Exploring the relationship of drug BCS classification, food effect, and gastric pH-dependent drug interactions. AAPS J. 2021;24(1):16.

15. FDA Draft Guidance, Guidance for Industry: Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations. Published: Mar 2019. Accessed: Mar 2022.

16. "Metabolism and Transport, Drug Interaction Database", Department of Pharmaceutics, University of Washington. www.druginteractionsolutions.org. Accessed: May 2009.

17. FDA. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available from http://courses.washington.edu/medch527/PDFs/Literature/527_fdatable.pdf. Accessed: Mar 2022:

18. Daly AK, Rettie AE, Fowler DM, et al. Pharmacogenomics of CYP2C9: functional and clinical considerations. J Pers Med 2017;8(1):1-31.