A PHASE 1, RANDOMIZED, OPEN-LABEL, 4-PERIOD, 5-TREATMENT, 6-SEQUENCE, CROSSOVER, SINGLE-DOSE STUDY IN HEALTHY PARTICIPANTS TO INVESTIGATE THE EFFECT OF TABLET FORMULATION AND FOOD ON THE BIOAVAILABILITY OF PF-07104091

Study Intervention Number:	PF-07104091
Study Intervention Name:	N/A
US IND Number:	CCI [redacted]
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4161007
Phase:	1

Brief Title: A Phase 1, Single-dose, Relative Bioavailability Study to Investigate the Effect of Tablet Formulation and Food on PF-07104091 Pharmacokinetics in Healthy Participants.

Document History

Document	Version Date
Original protocol	21 April 2022

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Open-label, 4-period, 5-treatment, 6-sequence, Crossover, Single-Dose Study in Healthy Participants to Investigate the Effect of Tablet Formulation and Food on the Bioavailability of PF-07104091

Brief Title: A Phase 1, Single-dose, Relative Bioavailability Study to Investigate the Effect of Tablet Formulation and Food on PF-07104091 Pharmacokinetics in Healthy Participants

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Rationale:

PF-07104091 is an inhibitor of CDK2 that is currently being investigated in a Phase 1 study (C4161001) in participants with tumor types that have potential to have increased CCNE1 expression/CDK2 activity and/or loss of the Rb tumor suppressor. Specific targeting of CDK2 represents a novel approach to address additional high unmet medical need indications such as HR-positive HER2-negative BC, NSCLC, ovarian cancer, and TNBC. To date, clinical drug supplies of PF-07104091 have used an early development enabling formulation that is an IR MST formulation with an API of PF-07104091 monohydrate. As the clinical development program of PF-07104091 is preparing to move to later stages of development, requiring the scaling-up and refinement of the investigational drug supply, activities are underway to further develop and optimize the manufactured PF-07104091 drug product.

The purpose of the study is to investigate the relative bioavailability of 4 tablet formulations of PF-07104091 and to characterize the effect of food on a PF-07104091 CCI [redacted] formulation. The data generated from this study will be used to guide selection of the tablet manufacturing method used for the drug supply of future Phase 3 studies, to inform dose administration instructions for PF-07104091 with regards to dosing with or without food, and to provide clinical PK supporting information to investigate the potential for identifying an in-vitro dissolution safe space for PF-07104091 that can inform the future optimization of PF-07104091 drug products.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the bioavailability of a single 300 mg dose of the PF-07104091 CCI formulation relative to a single 300 mg dose of the PF-07104091 CCI formulation under fasted conditions in adult healthy participants. • To estimate the bioavailability of a single 300 mg dose of the PF-07104091 CCI formulation and a single 300 mg dose of the PF-07104091 CCI formulation relative to a single 300 mg dose of the PF-07104091 CCI under fasted conditions in adult healthy participants.	• Plasma AUC_{inf} and C_{max} for PF-07104091. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
Secondary:	**Secondary:**
• To estimate the effect of a high-fat, high-calorie meal on the bioavailability of a single 300 mg dose of the PF-07104091 CCI formulation relative to fasted conditions in adult healthy participants. • To estimate the bioavailability of a single 300 mg dose of the PF-07104091 CCI formulation relative to a single 300 mg dose of the PF-07104091 CCI formulation under fasted conditions in adult healthy participants.	• Plasma AUC_{inf} and C_{max} for PF-07104091. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
• To evaluate the safety and tolerability of PF-07104091 when administered as a tablet formulation to healthy participants under fasted and fed conditions.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, physical examinations, and 12-lead ECGs.

Overall Design:

A Phase 1, randomized, open-label, 4-period, 5-treatment, 6-sequence, crossover, single-dose study in healthy participants.

Number of Participants:

Approximately 30 participants (5 participants per sequence) will be enrolled to study intervention. If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective(s), additional

participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. 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.

Intervention Groups and Duration:

Sequence	Period 1	Washout: at least 5 days between PF-07104091 doses	Period 2	Washout: at least 5 days between PF-07104091 doses	Period 3	Washout: at least 5 days between PF-07104091 doses	Period 4
1 (n=5)	A		B		C		D
2 (n=5)	B		C		A		D
3 (n=5)	C		A		B		D
4 (n=5)	A		B		C		E
5 (n=5)	B		C		A		E
6 (n=5)	C		A		B		E

Treatment A: 300 mg (2 × 125 mg and 2 × 25 mg) CCI .
Treatment B: 300 mg (2 × 125 mg and 2 × 25 mg) CCI .
Treatment C: 300 mg (4 × 75 mg) CCI .
Treatment D: 300 mg (4 × 75 mg) CCI .
Treatment E: 300 mg (4 × 75 mg) CCI .

There will be a minimum 5-day washout period between successive PF-07104091 doses.

Blood samples for PF-07104091 PK analysis will be collected predose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post the PF-07104091 dose in each period.

Participants will be on the study for up to 11 weeks, including the screening and follow-up periods. Participants will be screened within 28 days prior to the first dose of the IP and if all entry criteria are fulfilled, the participants will report to the PCRU on the day prior to Day 1 dosing (Day -1) of each period. For Treatments A, B, C, and D, following an overnight fast of at least 10 hours, and after the collection of the pre-dose PF-07104091 PK sample on Day 1 of each period, participants will be administered a 300 mg dose of PF-07104091. For Treatment E, after an overnight fast of at least 10 hours and after the collection of the pre-dose PF-07104091 PK sample on Day 1, participants will receive a high-fat and high-calorie breakfast 30 minutes prior to dosing. At least 80% of the full meal must be consumed prior to administration of PF-07104091. PF-07104091 will be administered as intact tablets with approximately 240 mL of ambient temperature water. Tablets will be swallowed and not chewed.

Following administration of PF-07104091, participants will be confined in the PCRU for a minimum of 2 days until completion of the 48-hour PK sample collection and discharge assessments on Day 3 in each period, or at the discretion of the investigator participants

could remain admitted to the PCRU throughout study conduct and discharged on Day 3 of Period 4. Participants will be discharged at the discretion of the investigator. A follow-up phone call will be made at least 28 calendar days and up to 35 calendar days after the last administration of the study intervention to capture any potential AEs and confirm appropriate contraceptive usage.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

1. Healthy adult males.

Exclusion Criteria

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

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

    - 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.

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.

    - Concomitant use of any medications or substances that are strong inducers or inhibitors of CYP3A4 or UGT1A9 are prohibited within 28 days prior to first dose of PF-07104091 and within 2 days after the last dose of study intervention, inclusive.

4. Current use of any prohibited concomitant medication(s) or participant unwilling/unable to use a permitted concomitant medication(s).

5. 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).

6. A positive urine drug test.

7. 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.

8. 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.

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

- AST **or** ALT level > ULN;
- Total bilirubin level ≥1.5 × 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 <60 mL/min/1.73 m^2 based on the CKD-EPI equation;
- Blood Calcium or Potassium <0.9 x LLN or >1.1 x ULN;
- Absolute neutrophil count <0.8 x LLN.

10. 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) 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).

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

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

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

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

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

Statistical Methods:

For treatment comparisons addressing the primary objectives of the study, natural log transformed AUC_{inf} (if data permits), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within a 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.

For treatment comparisons addressing the secondary objectives of the study (where each treatment comparison occurs via fixed-sequence), 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 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.

Pharmacokinetics Analysis

The PK concentration population is defined as all participants randomized and treated who have at least 1 PF-07104091 concentration in at least 1 treatment period.

The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PF-07104091 PK parameters of primary interest in at least 1 treatment period.

PK parameters for PF-07104091 will be analyzed using standard noncompartmental methods of analysis. Actual PK sampling times will be used in the derivation of PF-07104091 PK parameters when available, otherwise nominal times will be used. The PF-07104091 plasma PK parameters will be summarized descriptively by Treatment. Plasma concentrations will be listed and summarized descriptively by Treatment, and nominal PK sampling time. Individual participant and summary profiles (mean and median plots) of the plasma concentration time data will be plotted using actual and nominal times, respectively.

Safety Analysis

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

Ethical Considerations:

PF-07104091 will not provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of PF-07104091. Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. Taking into account the measures to minimize risk to participants, the potential risks associated with PF-07104091 are justified by the anticipated benefits that may be afforded by furthering the understanding of PF-07104091.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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

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

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screening**[a]	**Periods 1-4**																**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**[b]	**Day 1**												**Day 2**		**Day 3**	**28-35 Days**[c]	
Hours After Dose			Pre-dose	0	0.5	0.75	1	1.5	2	3	4	6	8	12	24	36	48		
Informed consent	X																		
PCRU confinement[d]		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		
Inclusion/exclusion criteria[e]	X	X																	
Medical/medication history (update)[f]	X	X																	
Demography[g]	X																		
Physical examination[h]	X	X															X[i]		X
Safety laboratory[j]	X	X[j]	X[j]														X[j]		X
Urine drug screening/Urine cotinine/Alcohol breath test[k]	X	X																	
Serology: HBsAg, HBsAb, HBcAb, HCVAb, and HIV[l]	X																		
Contraception check[m]	X	X																X	X
12-lead ECG (single)[n]	X		X[o]														X[o]		X
Vital signs (BP/PR/RR)[p]	X	X	X[o]														X[o]		X
CCI [redacted]		[redacted]																	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]							[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]																	[redacted]		[redacted]
[redacted]																	X[i]		X
COVID-19 questionnaire[q]	X	X																	

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screening**[a]	**Periods 1-4**															**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**[b]	**Day 1**												**Day 2**		**Day 3**	**28-35 Days**[c]	
Hours After Dose			Pre-dose	0	0.5	0.75	1	1.5	2	3	4	6	8	12	24	36	48		
COVID-19 testing[r]	X	X																	
COVID-19 check temperature[s]	X	X	X[o]														X[o]		
PF-07104091 dosing[t]				X															
Breakfast[v]			X[v]																
PK Blood Sampling for PF-07104091[w]			X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Retained Research Sample for Genetics (Prep D1)[x]			X																
Other Retained Research Samples (Prep B2)[x]			X																
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Concomitant treatments	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		X
PCRU discharge																	X[i]		

a. Screening will be performed within 28 days prior to the first dose of PF-07104091.
b. This is applicable for each check-in to the PCRU, unless particularly specified.
c. Follow-up contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.
d. Participants will be admitted to the PCRU on Day -1 of each period. Participants may be discharged on Day 3 of each period at the discretion of the investigator following the completion of all Day 3 assessments, or at the discretion of the investigator participants could remain admitted to the PCRU throughout study conduct and discharged on Day 3 of Period 4.
e. Inclusion/exclusion criteria will be reviewed at Screening and at the Day -1 check-in for Period 1.
f. Medical history will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days prior to first dose of PF-07104091. Medical history will be recorded at Screening and updated on Period 1 Day -1.
g. Demographics will include participant race, ethnicity, age, gender, height, and weight during the Screening visit.
h. Physical exam will be performed by trained medical personnel at the PCRU at Screening or Period 1 Day -1 only (height and weight must be obtained at Screening to obtain BMI for eligibility criteria). A brief physical examination will be performed prior to discharge from the PCRU and may be performed at other designated time points at the discretion of the investigator.
i. This will be applicable for discharge day from the PCRU (could be Day 3 in each period or only at Day 3 of Period 4 at discretion of investigator, and prior to early termination/discontinuation if applicable).
j. Safety laboratory assessments including hematology, chemistry, and urinalysis will be performed at Screening, prior to dosing in each treatment period (can be Day -1 or pre-dose on Day 1 at discretion of investigator), and prior to each discharge from the PCRU (could be Day 3 in each period or only at Day 3 of Period 4 at discretion of investigator), and prior to early termination/discontinuation if applicable. All the safety laboratory samples must be collected following at least a 4-hour fast. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator.

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screening**[a]	**Periods 1-4**																**Follow-Up**	**Early Termination/ Discontinuation**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**[b]	**Day 1**													**Day 2**		**Day 3**	**28-35 Days**[c]	
Hours After Dose			Pre-dose	0	0.5	0.75	1	1.5	2	3	4	6	8	12	24	36	48		

k. Urine drug and urine cotinine (mandatory) and alcohol breath test (at discretion of investigator) will be performed at Screening, on Period 1 Day -1, and upon PCRU check-in on Day -1 of each subsequent period. These tests may be performed at any other time at the discretion of the investigator.
l. HBsAb will be tested if HBsAg and/or HBcAb are positive.
m. 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.
n. Single 12-lead ECG readings will be taken at approximately the specified time point. All ECG assessments will be made after at least a 5-minute rest in a supine position and prior to any blood draws or vital sign measurements. Additional ECGs may be taken at any time at the discretion of the investigator.
o. This will be done pre-dose of Day 1 and also on Day 3 of each treatment period.
p. Single supine BP, RR and PR will be performed following at least a 5-minute rest in a supine position, at specified time point. BP, RR and PR assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time.
q. Check exposure to positive participant, residence or travel in area of high incidence, and COVID-19 related signs and symptoms as per local requirements.
r. The testing for COVID-19 pathogen by RT-PCR will be performed at specified time point and an additional SARS-CoV-2 test will also be performed after 4 days (ie, upon completion of 4 × 24 hours in house), ie, Period 1 Day 4. Additional testing for COVID-19 pathogen will also be done as per local requirements or by the Principal Investigator.
s. Temperature measurements may be done more frequently as clinically warranted.
t. PF-07104091 will be administered orally after overnight fasting of at least 10 hours on Day 1 of each treatment period for Treatments A, B, C, and D. There will be at least a 5-day washout between each dose of PF-07104091.
v. For Treatment E only, following an overnight fast of at least 10 hours and after the collection of the predose PF-07104091 PK sample on Day 1, participants will start the recommended high-fat (approximately 50% of total caloric content of the meal) high-calorie (approximately 800-1000 calories with 150, 250, and 500-600 calories from protein, carbohydrate and fat, respectively) breakfast 30 minutes prior to administration of PF-07104091. Breakfast will be consumed within an approximately 20 minute period with PF-07104091 administered approximately 10 minutes after completion of the meal. At least 80% of the full meal must be consumed prior to administration of PF-07104091.
w. Blood samples (~3 mL) for PK analysis of PF-07104091 will be taken at predose (within approximately 1 hour prior to PF-07104091 dosing), 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose. If ECG and BP/PR assessments are scheduled at the same nominal time point as a PK sample, PK samples should be collected after completion of these assessments.
x. Prep D1 Retained Research Samples for Genetics and Prep B2: 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 in Period 1 only.

2. INTRODUCTION

PF-07104091 is an inhibitor of CDK2 that is currently being investigated in a Phase 1 study (C4161001) in participants with tumor types that have potential to have increased CCNE1 expression/CDK2 activity and/or loss of the Rb tumor suppressor.

2.1. Study Rationale

The purpose of the study is to investigate the relative bioavailability of 4 tablet formulations of PF-07104091 and to characterize the effect of food on a PF-07104091 CCI formulation. The data generated from this study will be used to guide selection of the tablet manufacturing method used for the drug supply of future Phase 3 studies, to inform dose administration instructions for PF-07104091 with regards to dosing with or without food, and to provide clinical PK supporting information to investigate the potential for identifying an in-vitro dissolution safe space for PF-07104091 that can inform the future optimization of PF-07104091 drug products.

2.2. Background

PF-07104091 is an inhibitor of CDK2 that is currently being investigated in a Phase 1 study (C4161001) in participants with tumor types that have potential to have increased CCNE1 expression/CDK2 activity and/or loss of the Rb tumor suppressor. Specific targeting of CDK2 represents a novel approach to address additional high unmet medical need indications such as HR-positive HER2-negative BC, NSCLC, ovarian cancer, and TNBC. To date, clinical drug supplies of PF-07104091 have used an early development enabling formulation that is an CCI with an API of PF-07104091 monohydrate. As the clinical development program of PF-07104091 is preparing to move to later stages of development, requiring the scaling-up and refinement of the investigational drug supply, activities are underway to further develop and optimize the manufactured PF-07104091 drug product.

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-07104091 can be found in the current IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

PF-07104091 demonstrated a moderate to high CLp with extraction ratios of 0.56 to 0.72, when compared to hepatic blood flow across these species[1] and a moderate Vss (1.1 to 4.1 L/Kg) following IV dosing resulting in $t_{½}$ values ranging from 0.9 to 9.0 hours in mice, rats, dogs, and monkeys. Following oral dosing, PF-07104091 was rapidly absorbed in these species and exhibited moderate to high absorption (fa*fg ~ 0.6-1.0), with oral bioavailability ranging from 19% to 50%. In repeat dose toxicity studies, systemic exposures of PF-07104091 increased with increasing dose in mice and dogs. PF-07104091 exhibited moderate binding to plasma proteins (f_u between 0.211 and 0.495; 0.278 in human plasma) across the species evaluated (mouse, rat, monkey, dog, and human plasma). Blood-to-plasma ratios of PF-07104091 indicated preferential distribution of PF-07104091 into plasma over blood cells in all species except dog and monkey, in which PF-07104091 equally distributed into blood or plasma cells.

In vitro and in vivo, the primary metabolic pathways of PF-07104091 were O-demethylation, O-demethylation with subsequent oxidation, hydroxylation, and N-glucuronidation. All metabolites generated in human in vitro systems were also generated in one or more of the evaluated toxicology species (both in vitro and in vivo matrices) indicating that there were no human-unique metabolites. Preliminary in vitro studies indicated metabolic clearance of PF-07104091 was primarily mediated by CYP3A and UGT1A9. The primary metabolic pathways of PF-07104091 were determined in vitro in liver microsomes and hepatocyte systems in mouse, rat, rabbit, dog, monkey, and human. The metabolism of PF-07104091 was also profiled in vivo in rats (plasma, urine and bile), mice (plasma) and dogs (plasma and urine). CYP and UGT phenotyping studies were conducted in pooled human liver microsomes and hepatocytes, and recombinant CYP and UGT results were used as qualitative support of the HLM fm estimations. Based on the collective results obtained in these studies, CYP3A4/5 and UGT1A9 are predicted to be major contributors to the in vitro metabolism of PF-07104091. In a CYP3A5 *3/*3 PM population, the fm values for CYP 3A4/5, UGT1A9, and other remaining CYPs were 0.48, 0.46, and 0.06, respectively. In a CYP3A5 *1/*1 EM population, the fm values for CYP3A4, CYP3A5, UGT1A9, and other remaining CYP isoforms were 0.31, 0.35, 0.30, and 0.04 respectively. In the clinic, CYP3A5 EM populations may exhibit a higher plasma clearance of PF-07104091 compared to the CYP3A5 PM population.

Renal excretion of unchanged PF-07104091 was limited in rats, dogs, and monkeys, and biliary excretion was minimal in rats.

PF-07104091 has the potential to inhibit UGT1A1, UGT1A9, hBCRP (intestine and systemic), and OCT1 as well as intestinal MDR1 (P-gp) at clinically relevant concentrations. PF-07104091 exhibited negligible reversible inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 (IC_{50} >100 μM) in human liver microsomes and was not a time-dependent inhibitor of any of these CYP enzymes. The risk of clinically significant CYP reversible or TDI by PF-07104091 at clinically relevant concentrations is minimal. PF-07104091 did not cause induction of CYP1A2, CYP2B6, and CYP3A4 activity or mRNA up to 5 μM. Therefore, the potential for PF-07104091 to cause risk for DDI due to induction of CYP1A2, CYP2B6, and CYP3A4 at clinically relevant concentrations is low.

Additional information of the nonclinical PK and metabolism of PF-07104091 is available in the current IB.

2.2.3. Nonclinical Safety

The toxicity profile of PF-07104091 was assessed in exploratory and pivotal 1-month GLP toxicity studies in mice and dogs. The STD_{10} and NOAEL in mice were 300 (150 BID) and 150 (75 BID) mg/kg/day, respectively, while the HNSTD/NOAEL in dogs was 30 (15 BID) mg/kg/day. The target organs identified were the large intestine (degeneration/necrosis and/or infiltration colon/cecum) and testes (seminiferous tubule degeneration) in both dogs and mice, and stomach (nonglandular hyperplasia, hyperkeratosis, necrosis, and/or erosion/ulcer), small intestine (mucosal degeneration/atrophy duodenum, jejunum, ileum), hematolymphopoietic (decreased cellularity/necrosis and myelofibrosis in the bone marrow, decreased thymic lymphoid cellularity, and increased extramedullary hematopoiesis in the

spleen), bone (necrosis femur and sternum), and female reproductive system (proliferation of karyocytomegalic cells, hemorrhage, cleaved ovum, pigment deposition and benign teratoma in ovaries; decidual reaction, dilation, and endometrial decidualization/ degeneration in the uterus; increased mucosal mucification in the vagina) in mice.

PF-07104091 was assessed in a series of genetic toxicity assays. All in vitro studies were conducted with and without exogenous metabolic activation using concentrations up to those limited by cytotoxicity, insolubility, or the acceptable limits of the test system. PF-07104091 was negative for mutagenicity in the GLP microbial reverse mutation assays. PF-07104091 was positive in an exploratory in vitro micronucleus assay under all conditions tested. A fluorescent in situ hybridization assay with kinetochore probes demonstrated an aneugenic mechanism. In addition, PF-07104091 induced an increase in micronuclei in peripheral blood reticulocytes at >150 mg/kg/day in the mouse 1-month GLP toxicity study. Based on the C_{max} in mice at the NOEL dose (150 mg/kg/day) there is a 11x safety margin relative to the C_{max} in humans at the 300 mg dose. PF-07104091 is therefore considered non-genotoxic at clinically relevant exposures.

PF-07104091 showed limited activity in secondary pharmacology and cardiovascular ex vivo assays, including weak activity against the hERG channel (IC_{50} >300 μM). PF-07104091 did not demonstrate any cardiovascular effects (ECG or histopathology) in the pivotal dog study. In a GLP dog telemetry cardiovascular safety study, PF-07104091 administration resulted in small changes in hemodynamic parameters (SBP, DBP, MBP, HR); these findings were relatively short in duration lasting a few hours after the first or second dose, and with acute dosing are not considered a safety risk in healthy volunteers. Relative to the C_{max} at the human dose of 300 mg, the NOEL for cardiovascular effects was 0.5x and minimal effects were observed up to 3.8x.

In a GLP neuropulmonary safety study in mice, PF-07104091 administration resulted in lower locomotor activity during the first 30 min post dose and lower respiratory rate and minute volume with higher tidal volume between 30- and 240-minute post dose. These effects were minimal and transient and therefore are not considered a safety risk in healthy volunteers. Relative to the C_{max} at the human dose of 300 mg, the NOEL for neuropulmonary effects was 2x and minimal effects were observed between 8 and 24x.

Additional information of the nonclinical safety of PF-07104091 is available in the current IB.

2.2.4. Clinical Overview

PF-07104091 is currently being evaluated in an ongoing FIH open-label, multi-center, non-randomized Phase 1/2a study (Study C4161001) to investigate the safety, tolerability, PK, PD, and potential anti-tumor activity of single agent PF-07104091 and in combination with ET for patients with previously treated metastatic ER+/HER2- BC. Included in this Clinical Overview are summaries of the interim results of the ongoing Study C4161001.

2.2.4.1. Safety Overview

As of 30 September 2021, 24 patients have been treated with single agent PF-07104091 administered continuously BID across 7 dose levels (75-500 mg). All patients experienced at least 1 TEAE. The most frequently reported (≥20%) all causality TEAEs across all doses were nausea (77.3%), diarrhea (54.5%), fatigue (50.0%), vomiting (45.5%), hypokalemia (36.4%), anemia (31.8%), decreased appetite (31.8%), hyperuricemia (27.3%), and hypercalcemia (22.7%). The most frequently reported (≥5%) Grade 3 or higher all causality TEAEs were nausea (22.7%), fatigue and hypokalaemia (18.2% each), diarrhea and neutrophil count decreased (13.6% each), and WBC count decreased (9.1%). All-causality TEAEs reported were mainly of severity Grade 3 or lower. One Grade 4 all-causality TEAE (Neutropenia) was reported at the 500 mg BID dose. No Grade 5 all-causality TEAEs were reported during the study.

The most frequently reported (≥10% of patients) treatment-related TEAEs of any grade were nausea (72.7%), diarrhea, and vomiting (45.5% each), fatigue (40.9%), anemia (27.3%), decreased appetite and hypokalemia (22.7% each), hyperuricemia (18.2%), alopecia, hypercalcemia, neutrophil count decreased, platelet count decreased, and rash (13.6% each). The most frequently reported (≥5% of patients) Grade 3 or higher treatment related TEAEs were nausea (22.7%), hypokalemia (18.2%), and neutrophil count decreased, diarrhea, and fatigue (13.6% each). No Grade 5 treatment related TEAEs were reported. First-cycle DLTs (cycle is 28 days in duration, with PF-07104091 administered BID orally on days 1 to 28 of each cycle) were reported in 5 patients: Grade 3 fatigue in 1 patient treated at 300 mg BID; Grade 3 nausea and Grade 3 decreased appetite in 2 patients treated at 375 mg BID; Grade 3 worsening of diarrhea and Grade 3 fatigue in 2 patients treated at 500 mg BID.

The doses 500 mg BID and 375 mg BID were evaluated as not tolerable. Based on the available clinical data, AESIs include gastrointestinal toxicities (such as nausea, vomiting and diarrhea), and hematological toxicities (including anemia and neutropenia). The MTD/ RDE has been determined as 300 mg BID.

Further details on the clinical safety information with PF-07104091 are provided in the current IB.

2.2.4.2. Summary of PF-07104091 Pharmacokinetics in Humans

In the ongoing Phase 1 study C4161001, as of 08 October 2021, preliminary concentration-time data of PF-07104091 following single and multiple oral administration at 75 mg BID to 500 mg BID were available from 24 participants with advanced solid tumors and HR-positive HER2-negative advanced or metastatic breast cancer. The preliminary concentration-time data were analyzed by noncompartmental approach using nominal PK sampling times.

PF-07104091 was rapidly absorbed following oral administration at doses up to 375 mg BID, with a median T_{max} by dose level of 1.5 to 4 hours (range 0.5 – 8 hours). Single dose and multiple dose (Day 15) C_{max} and AUC_{last} demonstrated dose-dependent increases across the dose range of 75 mg to 500 mg BID. The average effective half-life estimated from the PK

sample collections out to 9 hours post-dose was approximately 2 to 4 hours. However, the moderate accumulation (mean R_{ac} by dose level from 75 mg to 300 mg BID ranged from 1.78 to 2.01) following repeated BID administration suggests a longer terminal elimination half-life.

Further details on the clinical PK of PF-07104091 are provided in the current IB.

2.3. Benefit/Risk Assessment

PF-07104091 will not provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, metabolism, and elimination of PF-07104091. Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. Taking into account the measures to minimize risk to participants, the potential risks associated with PF-07104091 are justified by the anticipated benefits that may be afforded by furthering the understanding of PF-07104091.

Study C4161007 is the first time that PF-07104091 will be administered to healthy adult participants. Prior to this study, PF-07104091 has been administered as monotherapy or in combination with other anti-cancer agents to advanced cancer patients at doses ranging from 75 mg to 500 mg BID continuously. Based on the results of the nonclinical toxicity studies (Section 2.2.3), the potential risk of PF-07104091 administration to healthy participants can be managed adequately, and be mitigated with preventive measures in place that includes routine monitoring of adverse events and changes in clinical laboratory test parameters for clinical management, including study drug discontinuation as appropriate to ensure the safety of the study participant. Based on the available data from Study C4161001, the clinical safety profile favors further development of PF-07104091.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07104091 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-07104091		
Potential effects of PF-07104091 on fertility, pregnancy, and lactation.	At this time, it is not known whether PF-07104091 can cause fetal harm when administered to pregnant women. Animal reproductive studies have not been conducted with PF-07104091. It is also not known whether PF-07104091 can affect male or female fertility, or whether PF-07104091 is secreted in human milk. PF-07104091 did cause testicular toxicity in mice and dogs and effects in female reproductive organs in mice, and therefore, may potentially impact fertility.	Eligibility criteria and the contraceptive lifestyle requirements for this protocol have been crafted to mitigate these identified potential risks. Women are excluded from participation in this trial and male participants will be instructed and monitored on the contraceptive requirements implemented to minimize potential risks.
Potential phototoxicity effects of PF-07104091.	PF-07104091 absorbs in the UVA-UVB/visible range from 290-400 nm with a calculated MEC of >1000 L/(mol cm) and, as a result, could have photo safety risks.	The lifestyle guidelines for this protocol include participant instructions to limit exposure to sunlight/high intensity ultraviolet light and use sunscreen products with high sun protection factor.
Potential risks associated with PF-07104091 include the following: gastrointestinal toxicities (such as nausea, vomiting and diarrhea), and hematological toxicities (including anemia and neutropenia).	The potential risks are based on emerging clinical data from the ongoing Study C4161001 following continuous administration of PF-07104091 to advanced cancer patients at doses ranging from 75 to 500 mg BID.	The present study will test single doses of PF-07104091 and implement a washout period between doses across treatment periods to minimize exposure of PF-07104091 in the healthy participants. AEs and clinical laboratory results will be monitored on an ongoing basis.
Study Procedures		
Blood draws for assessment of PK, safety labs, and retained samples.	A blood draw may cause participant discomfort including faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.	Blood draws will be performed by experienced and trained site staff within the confines of the PCRU.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific assessments according to the Schedule of Activities.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the bioavailability of a single 300 mg dose of the PF-07104091 CCI [redacted] formulation relative to a single 300 mg dose of the PF-07104091 CCI [redacted] formulation under fasted conditions in adult healthy participants. • To estimate the bioavailability of a single 300 mg dose of the PF-07104091 CCI [redacted] formulation and a single 300 mg dose of the PF-07104091 CCI [redacted] formulation relative to a single 300 mg dose of the PF-07104091 CCI [redacted] formulation under fasted conditions in adult healthy participants.	• Plasma AUC_{inf} and C_{max} for PF-07104091. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
Secondary:	**Secondary:**
• To estimate the effect of a high-fat, high-calorie meal on the bioavailability of a single 300 mg dose of the PF-07104091 CCI [redacted] formulation relative to fasted conditions in adult healthy participants. • To estimate the bioavailability of a single 300 mg dose of the PF-07104091 CCI [redacted] formulation relative to a single 300 mg dose of the PF-07104091 CCI [redacted] formulation under fasted conditions in adult healthy participants.	• Plasma AUC_{inf} and C_{max} for PF-07104091. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
• To evaluate the safety and tolerability of PF-07104091 when administered as a tablet formulation to healthy participants under fasted and fed conditions.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, physical examinations, and 12-lead ECGs.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

A Phase 1, randomized, open-label, 4-period, 5-treatment, 6-sequence, crossover, single-dose study in healthy participants. This study will consist of 5 treatments:

- Treatment A: Single 300 mg dose (2 × 125 mg and 2 x 25 mg) of CCI [redacted] under fasting conditions (following an overnight fast of at least 10 hours).
- Treatment B: Single 300 mg dose (2 × 125 mg and 2 x 25 mg) of CCI [redacted] under fasting conditions (following an overnight fast of at least 10 hours).
- Treatment C: Single 300 mg dose (4 × 75 mg) of CCI [redacted], under fasting conditions (following an overnight fast of at least 10 hours).
- Treatment D: Single 300 mg dose (4 × 75 mg) of CCI [redacted] under fasting conditions (following an overnight fast of at least 10 hours).
- Treatment E: Single 300 mg dose (4 × 75 mg) of CCI [redacted], given with a high-fat/high-calorie meal.

Approximately 30 participants (5 participants per sequence) will be enrolled to study intervention. If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective(s), additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. 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.

Each enrolled participant will receive one of the 5 treatments in each period according to the treatment schedule shown in Table 1. A minimum 5 day washout period between successive single doses of PF-07104091 is included to minimize any residual PF-07104091 concentrations prior to start of the next treatment period. For Treatments A, B, C, and D, following an overnight fast of at least 10 hours, and after the collection of the pre-dose PF-07104091 PK sample on Day 1 of each period, participants will be administered a 300 mg dose of PF-07104091. For Treatment E, after an overnight fast of at least 10 hours and after the collection of the pre-dose PF-07104091 PK sample on Day 1, participants will receive a

high-fat and high-calorie breakfast approximately 30 minutes prior to dosing. At least 80% of the full meal must be consumed prior to administration of PF-07104091. PF-07104091 will be administered as intact tablets with approximately 240 mL of ambient temperature water. Tablets will be swallowed and not chewed. In each period, participants will undergo blood sampling for determination of PF-07104091 PK at predose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours following PF-07104091 administration. Participants who withdraw may be replaced at the joint discretion of the investigator and the sponsor.

Table 1. Treatment Schedule

Sequence	Period 1	Washout: at least 5 days between PF-07104091 doses	Period 2	Washout: at least 5 days between PF-07104091 doses	Period 3	Washout: at least 5 days between PF-07104091 doses	Period 4
1 (n=5)	A		B		C		D
2 (n=5)	B		C		A		D
3 (n=5)	C		A		B		D
4 (n=5)	A		B		C		E
5 (n=5)	B		C		A		E
6 (n=5)	C		A		B		E

Treatment A: 300 mg (2 × 125 mg and 2 × 25 mg) CCI [redacted].
Treatment B: 300 mg (2 × 125 mg and 2 × 25 mg) CCI [redacted]
Treatment C: 300 mg (4 × 75 mg) CCI [redacted].
Treatment D: 300 mg (4 × 75 mg) CCI [redacted]
Treatment E: 300 mg (4 × 75 mg) CCI [redacted].

Participants will be on the study for up to 11 weeks, including the screening and follow-up periods. Participants will be screened within 28 days prior to the first dose of investigational product in Period 1. Participants will be admitted to the PCRU on Day -1 and will be required to remain in the PCRU for a minimum of 3 days until completion of 48 hours PK sampling on Day 3. The investigator could choose to confine participants in the PCRU beyond Day 3 and discharge them following completion of Day 3 assessments in Period 4. Alternatively, participants will be eligible for discharge from the PCRU at 48 hours post-dose in each period following review of the discharge safety assessments, provided that the participants are able to return to the PCRU on Day -1 for each of the remaining study periods. If a participant has any clinically significant study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the PCRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. A follow-up contact will be completed at least 28 calendar days and up to 35 calendar days after the last administration of PF-07104091 to capture any potential AEs and to confirm appropriate contraception usage. Contact with the participant may be done via a phone call.

4.2. Scientific Rationale for Study Design

The purpose of the study is to investigate the relative bioavailability of 4 tablet formulations of PF-07104091 and to characterize the effect of food on a PF-07104091 CCI [redacted] tablet formulation. The data generated from this study will be used to guide selection of the tablet

manufacturing method used for the drug supply of future Phase 3 studies, to inform dose administration instructions for PF-07104091 with regards to dosing with or without food, and to provide clinical PK supporting information to investigate the potential for identifying an in-vitro dissolution safe space for PF-07104091 that can inform the future optimization of PF-07104091 drug products.

The CCI [redacted] formulation is representative of the drug product that has been used in the PF-07104091 early development program to date. The CCI [redacted] and CCI [redacted] are drug products that are being evaluated as prototypes for the drug supplies of upcoming later stage studies. The primary objectives of this study are to estimate the relative bioavailability of these 3 tablet formulations of PF-07104091 to inform and de-risk the drug product supply strategy for the PF-07104091 clinical development program.

PK of the CCI [redacted] formulation relative to the potential Phase 3 target formulations will be evaluated as a secondary objective of this study to investigate the effect of dissolution rate on the bioavailability of PF-07104091. This data will enable investigating the potential to establish a dissolution rate clinical safe space that could guide future optimization of the PF-07104091 drug products. Data from this study may be used to develop correlations between in vitro dissolution and in vivo PK and to develop and validate a physiological based PK model for different dissolution rates. Such investigations would be described in separate reports outside of the study CSR.

PK of the CCI [redacted] formulation following administration of a standard high-fat/high-calorie meal will be evaluated as a secondary objective of this study to investigate the effect of food on the bioavailability of PF-07104091.

The study is being designed as a crossover study to minimize the potential for intrinsic factors that may impact inter-individual variability in the PK of PF-07104091 from confounding the comparisons of PK parameters across the treatment periods and better estimate the true differences between the study treatments. The study includes randomization to one of 6 sequences to account for any period or sequences effect in the comparison of the 3 treatments (Treatment A, Treatment B, and Treatment C) on which the primary objectives of the study are based. As the evaluation of Treatments D and E are secondary objectives of the study and to minimize participant exposures and potential for participant drop-out prior to study completion, each participant will be randomized to a sequence where in the fourth and final Treatment Period they will receive either Treatment D or Treatment E following completion of Treatment Periods corresponding to the primary objectives of the study.

Population-PK modelling of interim PK data emerging from the ongoing C4161001 study has been leveraged to identify appropriate washout periods between successive doses to minimize any residual PF-07104091 concentrations prior to start of the next treatment and to identify that the 48-hour duration of PK sampling post-dose is sufficient to enable reporting of the desired PK parameter endpoints.

4.2.1. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-07104091 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

The monotherapy MTD and RDE determined in Phase 1/2 Study C4161001 for PF-07104091 is 300 mg BID. This dose is lower than the highest dose evaluated in the Phase 1 C4161001 study (500 mg BID) and was found to be safe and well tolerated.

This study is designed to evaluate relative bioavailability of various PF-07104091 tablet formulations in healthy adult participants at the current recommended monotherapy therapeutic dose. Therefore, single oral 300 mg doses of PF-07104091 will be used in this relative bioavailability study. The anticipated exposures of PF-07104091 following administration of single 300 mg doses to adult healthy volunteers in this study provides sufficient safety exposure margins over the exposures observed at NOEL dose levels in the nonclinical safety studies (Section 2.2.3).

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 parts 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 must be male and 18 to 60 years of age, inclusive, at screening.

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

2. Male participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs, and standard 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. Evidence of a personally signed and dated ICD indicating that the participant has been informed of all pertinent aspects of the study.

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

   - 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.

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).

- Concomitant use of any medications or substances that are strong inducers or inhibitors of CYP3A4 or UGT1A9 are prohibited within 28 days prior to first dose of PF-07104091 and within 2 days after the last dose of study intervention, inclusive.

4. Current use of any prohibited concomitant medication(s) or participant unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

5. 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:

6. A positive urine drug test.

7. 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.

8. 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.

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

   - AST **or** ALT level > ULN;

- Total bilirubin level ≥1.5 × 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 <60 mL/min/1.73 m^2 based on the CKD-EPI equation;
- Blood Calcium or Potassium <0.9 x LLN or >1.1 x ULN;
- Absolute neutrophil count <0.8 x LLN.

Other Exclusion Criteria:

10. 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) 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).
11. Use of tobacco or nicotine containing products within 3 months of screening or a positive urine cotinine test (ie, active smokers and those who currently use nicotine-containing products are excluded from participation in this study).
12. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
13. History of sensitivity to heparin or heparin-induced thrombocytopenia.
14. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
15. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

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 10.4.3) 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 on Day 1 of each Period. No food will be allowed for at least 4 hours postdose on Day 1 in each Period.

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

- There will be no predose water restriction for the fed treatment periods (Treatment E) on Day 1. For Treatment E, participants will start the recommended high-fat/high-calorie breakfast 30 minutes prior to administration of PF-07104091. Breakfast will be consumed within an approximate 20 minute period with PF-07104091 administered approximately 10 minutes after completion of the meal. Participants will be encouraged to consume the high-fat/high-calorie breakfast in its entirety, however, as long as at least 80% of the full meal is consumed prior to administration of PF-07104091 it will not be considered a protocol deviation.

- Lunch will be provided approximately 4 hours after PF-07104091 dosing.

- Dinner will be provided approximately 9 to 10 hours after PF-07104091 dosing.

- An evening snack may be permitted.

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

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein (with the exception of the morning of Day 1 for Treatment E, when the recommended high-fat/high-calorie breakfast is provided). The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

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

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the PCRU 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 abstain from the use of tobacco- or nicotine-containing products until collection of the final PK sample for Period 4 or until early termination.

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 instructed to limit exposure to sunlight/high intensity ultraviolet light and use sunscreen products with high sun protection factor.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational, 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-07104091 tablets.

6.1. Study Intervention(s) Administered

For this study, the study interventions are the tablet formulations PF-07104091 administered at a total dose of 300 mg under fasted or fed conditions; Treatment A [2 × 125 mg and 2 × 25 mg CCI under fasting conditions], Treatment B [2 × 125 mg and 2 × 25 mg CCI under fasting conditions],

Treatment C [4 × 75 mg [redacted], under fasting conditions], Treatment D [4 × 75 mg [redacted] (slower dissolution), under fasting conditions], and Treatment E [4 × 75 mg [redacted] (moderate dissolution), given with a high-fat/high-calorie meal]. The PF-07104091 tablet formulations will be supplied by Pfizer.

PF-07104091 25, 75, and/or 125 mg tablets for the four tablet formulations will be supplied to the PCRU in bulk along with individual dosing containers for unit dosing. A brief description of the PF-07104091 formulations supplied in this study is provided in Table 2.

Table 2. Summary of PF-07104091 Formulations

Description	Label Names	Material ID/ Lot Number	Included in Treatment(s)	Route of Administration
PF-07104091 Monohydrate 25 mg Tablet	PF-07104091 25 mg [redacted]	[redacted]	Treatment A	Oral
PF-07104091 Monohydrate 125 mg Tablet	PF-07104091 125 mg [redacted]	[redacted]	Treatment A	Oral
PF-07104091 Monohydrate 25 mg Tablet	PF-07104091 25 mg [redacted]	[redacted]	Treatment B	Oral
PF-07104091 Monohydrate 125 mg Tablet	PF-07104091 125 mg [redacted]	[redacted]	Treatment B	Oral
PF-07104091 Monohydrate 75 mg Tablet Core	[redacted]	[redacted]	Treatment D	Oral
PF-07104091 Monohydrate 75 mg Tablet Batch Process	[redacted]	[redacted]	Treatment C, Treatment E	Oral

6.1.1. Administration

All Treatment Periods:

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

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing. If a participant vomits within 12 hours following administration of PF-07104091 in any treatment period, the start time of the initial vomiting event must be entered into the CRF.

Treatment A [300 mg, CCI fasting conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will take a single 300 mg dose (2 × 125 mg and 2 × 25 mg tablets) of the CCI tablet formulation of PF-07104091 at approximately 0800 hours (plus or minus 2 hours).

Treatment B [300 mg, CCI fasting conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will take a single 300 mg dose (2 × 125 mg and 2 × 25 mg tablets) of the CCI tablet formulation of PF-07104091 at approximately 0800 hours (plus or minus 2 hours).

Treatment C [300 mg, CCI fasting conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will take a single 300 mg dose (4 × 75 mg tablets) of the CCI tablet formulation of PF-07104091 at approximately 0800 hours (plus or minus 2 hours).

Treatment D [300 mg, CCI fasting conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will take a single 300 mg dose (4 × 75 mg tablets) of the CCI tablet formulation of PF-07104091 at approximately 0800 hours (plus or minus 2 hours).

Treatment E [300 mg, CCI fed conditions]:

Following an overnight fast of at least 10 hours and after the collection of the predose PK sample on Day 1, participants will start the recommended high-fat (approximately 50% of total caloric content of the meal) high-calorie (approximately 800-1000 calories with 150, 250, and 500-600 calories from protein, carbohydrate and fat, respectively) breakfast approximately 30 minutes prior to administration of a single 300 mg dose (4 × 75mg tablets) of the CCI tablet formulation of PF-07104091. Breakfast will be consumed within an approximately 20 minute period with study intervention administered approximately 10 minutes after completion of the meal. Participants will be encouraged to consume the high-fat/high-calorie breakfast in its entirety, however, as long as at least 80% of the full meal is consumed prior to administration of study intervention it will not be considered a protocol deviation. Percentage of the meal consumed will be documented in the CRF. PF-07104091 should be administered at approximately 0800 hours (plus or minus 2 hours).

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

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

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

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

6.2.1. Preparation and Dispensing

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

Study interventions will be prepared at the PCRU 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 prepared doses (with intended number of tablets of each dose strength) will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Dispensing will be performed in PCRU by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of IPs.

6.3. Assignment to Study Intervention

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

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

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

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

6.6. Dose Modification

No dose modification is anticipated.

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

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

6.8. Treatment of Overdose

For this study, any dose of PF-07104091 greater than 300 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for a PF-07104091 overdose.

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

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

6.9. Prior and Concomitant Therapy

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

As PF-07104091 is primarily metabolized by CYP3A4 and UGT1A9, as determined in in vitro studies, concomitant use of any medications or substances that are strong inducers or inhibitors of CYP3A4 are prohibited within 28 days prior to dosing of study intervention and within 2 days after the last dose of PF-07104091. Additionally, PF-07104091 is an inhibitor of UGT1A1. Therefore, medications highly dependent on UGT1A1 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events are not permitted during dosing of PF-07104091, through 5 days after the last dose of PF-07104091.

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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

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

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may be used without repeat collection, as appropriate.

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

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

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 270 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.2. Efficacy Assessments

Not applicable.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

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

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

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

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

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

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

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

8.3.2.2. Respiratory Rate

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

8.3.2.3. Temperature

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

8.3.3. Electrocardiograms

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

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

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

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

qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

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

8.3.4. Clinical Safety Laboratory Assessments

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

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

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 48 hours after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

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

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

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

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

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection by RT-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 or by the PI.

CCI [redacted]

CCI [redacted]

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 or participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

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

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

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.

Other examples include, but are not limited to:

- The administration of an incorrect study intervention;
- The administration of an incorrect total dosage or incorrect combination of tablet dose strengths

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

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

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

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

8.5. Pharmacokinetics

Blood samples of approximately 3 mL, to provide approximately 1.2 mL plasma, will be collected for measurement of plasma concentrations of PF-07104091 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 within the sampling time window specified in the SoA 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. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor. 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.

Samples will be used to evaluate the PK of PF-07104091. Samples collected for analyses of PF-07104091 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification, analysis of endogenous biomarkers, and/or evaluation of the bioanalytical method, CCI [redacted]

Samples collected for measurement of plasma concentrations of PF-07104091 will be analyzed using a validated analytical method in compliance with applicable SOPs.

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

Any 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.

8.6.2. Retained Research Samples for Genetics

A 4 mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

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

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.

8.7.4. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

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

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to the study intervention(s) and safety biomarkers. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

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

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.

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9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and 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. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
PK Concentration	The PK concentration population is defined as all participants randomized and treated who have at least 1 PF-07104091 concentration in at least 1 treatment period.
PK Parameter	The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PF-07104091 PK parameters of primary interest in at least 1 treatment period.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.3. Statistical Analyses

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

9.3.1. Pharmacokinetic Analyses

9.3.1.1. Derivation of Pharmacokinetic Parameters

Plasma PK parameters of PF-07104091 will be derived (as data permits) from the concentration-time data using standard noncompartmental methods as outlined in Table 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 3. Plasma PF-07104091 PK Parameters Definitions

Parameter	Definition	Method of Determination
AUC_{inf}*	Area under the concentration-time curve from time 0 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 and k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}$*	Terminal half-life	$Log_e(2)/k_{el}$ 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	$Dose/(AUC_{inf} \bullet k_{el})$

*If data permits.

The following supporting data from the estimation of $t_{½}$ will also be provided: the terminal phase rate constant (k_{el}); the goodness-of-fit statistic from the regression (r^2); the percentage of AUC_{inf} obtained by forward extrapolation (AUC_{extrap}%); and the first, last, and number of time points used in the estimation of k_{el} ($k_{el,t(lo)}$, $k_{el,t(hi)}$, and $k_{el,t(n)}$).

9.3.2. Statistical Methods for PK Data

For assessment of the primary objectives of the study (Periods 1, 2 and 3), natural log transformed AUC_{inf} (if data permits), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and participant within a 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. The following treatment comparisons will be performed:

- Treatment C (Test) vs Treatment B (Reference)
- Treatment B (Test) vs Treatment A (Reference)
- Treatment C (Test) vs Treatment A (Reference)

For the secondary objectives of the study (where each treatment comparison occurs via fixed-sequence), 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 fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. The following treatment comparisons will be performed:

- Treatment D (Test) vs Treatment C (Reference)
- Treatment E (Test) vs Treatment C (Reference)

PK parameters, including plasma AUC_{inf} (if data permits), AUC_{last}, CL/F (if data permits), C_{max}, T_{max}, $t_{½}$ (if data permits), and V_z/F (if data permits) of PF-07104091 will be summarized descriptively by Treatment. For AUC_{inf} (if data permits), AUC_{last} and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf} (if data permits), AUC_{last} and C_{max}, will be plotted by treatment.

The plasma concentrations of PF-07104091 will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales.

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

9.3.3. Other Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical 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.

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[redacted]

[redacted]

9.4. Interim Analyses

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

9.5. Sample Size Determination

A sample size of 30 PK evaluable participants in each cohort will provide 90% confidence intervals for the difference between treatments of ±0.181 on the natural log scale for both AUC_{inf} and C_{max}, with 90% coverage probability. The following table (Table 4) presents the width of 90% confidence interval for different estimated effects:

Table 4. Width of 90% CIs for Different Estimated Effects of Test/Reference Ratio

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf} / C_{max}	85.0%	70.93%, 101.86%	30.93%
	90.0%	75.10%, 107.85%	32.75%
	95.0%	79.27%, 113.85%	34.57%
	100.0%	83.45%, 119.84%	36.39%
	105.0%	87.62%, 125.83%	38.21%
	110.0%	91.79%, 131.82%	40.03%
	115.0%	95.96%, 137.81%	41.85%

These calculations are based on the estimates of within-participant standard deviation of 0.39 for both $\log_e AUC_{inf}$ and $\log_e C_{max}$, as obtained from clinical study C4161001.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

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

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

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and/or IQMP maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

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 (PCRU).

Description of the use of the computerized system is documented in Source Document Locator, which is maintained by the sponsor.

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.

10.1.9. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.10. Publication Policy

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

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

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

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

10.1.11. Sponsor's Medically Qualified Individual

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

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, 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 5. 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 Cystatin C and eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein For suspected DILI:[c] 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:[d] Creatinine (Scr) Cystatin C (Scys) eGFR (Scr only and combined Scr+Scys)	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[a]	Urine Cotinine At screening: • Urine drug screening[b] • Hepatitis B surface antigen • Hepatitis C antibody • Hepatitis B core antibody • HIV

a. Only if UTI is suspected and if either a) urine dipstick is positive for nitrites or leukocyte esterase or both, or b) when blood and/or protein are 1+ positive or greater.
b. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific). Urine drug screening will be performed at Screening, on Period 1 Day -1, and upon PCRU check-in on Day -1 of each subsequent period and may be performed at any other time at the discretion of the investigator.
c. See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.
d. See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and

stored for the duration of the study. CCI [redacted]

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 91 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) plus an additional 90 days (a spermatogenesis cycle):

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

- In addition to male condom use, the male participant should be advised of the benefit for a WOCBP partner using a highly effective method of contraception with a failure rate of <1% per year, as described in Section 10.4.3.

10.4.2. 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.

10.4.3. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable 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 + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Injectable + barrier*
8. Sexual Abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07104091 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

    - Retained samples will be stored indefinitely or for another period as per local requirements.

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

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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**
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**
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 KDIGO 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.

CCI [redacted]

[redacted]	
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	

		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]					
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[redacted]	[redacted]					
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[redacted]	[redacted]					
[redacted]	[redacted]					

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{extrap\%}$	the percentage of AUC_{inf} obtained by forward extrapolation
AUC_{inf}	area under the plasma-concentration time curve from time 0 to infinity
AUC_{last}	area under the plasma-concentration time curve from 0 to time of last measurable concentration
AV	atrioventricular
BBS	Biospecimen Banking System
BC	breast cancer
BID	twice daily
BMI	body-mass index
BP	blood pressure
CCNE1	cyclin E
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CL/F	apparent oral clearance
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{last}	last observed concentration
CLp	systemic plasma clearance
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CTIS	Clinical Trials Information System
CYP	cytochrome P450
DBP	diastolic blood pressure
DC	direct compression
DDI	drug-drug interaction

Abbreviation	Term
CCI	[redacted]
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DMC	data monitoring committee
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
ER+	estrogen receptor-positive
eSAE	electrionic serious adverse event
ET	endocrine therapy
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
f_a	the fraction of orally administered drugs absorbed from the intestine
f_g	intestinal availability
FIH	first-in-human
f_m	fraction of adinazolam converted to the N-demethyl metabolite
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBcAB	Hepatitis B core antibody
hBCRP	Human breast cancer resistance protein
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HER2	human epidermal growth factor receptor 2
hERG	the human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HLM	hierarchical linear model
HNSTD	highest non-severely toxic dose
HR	hormone-positive; heart rate
IB	Investigator's Brochure
IC_{50}	The half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IND	Investigational New Drug

Abbreviation	Term
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IQMP	Integrated Quality Management Plan
IR	immediate release
IRB	Institutional Review Board
IV	intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	first-order elimination rate constant
$k_{el,t(hi)}$	initial slope time point value used in the calculation of k_{el}
$k_{el,t(lo)}$	final slope time point value used in calculation of k_{el}
$k_{el,t(n)}$	number of time points used in the calculation of k_{el}
LBBB	left bundle branch block
LFT	liver function test
LLN	lower limit of normal
MBP	Mean Blood Pressure
MDR1 (P-gp)	multidrug resistance mutation 1
MEC	minimum essential coverage
MQI	medically qualified individual
MST	material-sparing tablet
MTD	maximum tolerated dose
NA	not applicable
NOAEL	no-observed-adverse-effect level
NOEL	No Observable Effect Level
NSCLC	non-small cell lung cancer
OCT1	organic cation transporter 1
PCRU	Pfizer clinical research unit
PD	pharmacodynamics
PK	pharmacokinetic(s)
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTcF	QTc corrected using Fridericia's formula
r^2	the goodness-of-fit statistic from the regression
R_{ac}	accumulation ratio based on AUC (observed)
RBC	red blood cell
Rb	retinoblastoma
RDE	recommended dose for monotherapy expansion
RR	respiratory rate
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
Scr	serum creatinine
Scys	Serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safe document
STD_{10}	severly toxic dose
ST-T	ST-segment and T-wave
SUSAR	Suspected Unexpected Adverse Reaction
$t_{1/2}$	terminal phase half-life
T bili	total bilirubin
THC	tetrahydrocannabinol
TDI	lactoferrin Versus Total Dose Infusion
TEAEs	treatment-emergent adverse event
T_{max}	time to C_{max}
TNBC	triple-negative breast cancer
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
UTI	urinary tract infection
UVA	ultraviolet A
UVB	ultraviolet B
Vss	steady-state volume of distribution
V_z/F	apparent volume of distribution during terminal phase
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

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