Title Page

AN INTERVENTIONAL, PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, 2-PERIOD STUDY TO EVALUATE THE EFFECT OF A SINGLE ORAL DOSE OF ARV-471 (PF-07850327) ON THE PHARMACOKINETICS OF ROSUVASTATIN IN HEALTHY PARTICIPANTS

Study Intervention Number:	PF-07850327
Study Intervention Name:	ARV-471
US IND Number:	CCI [redacted]
EudraCT/CTIS Number:	Not Applicable
ClinicalTrials.gov ID:	Not Applicable
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C4891029
Phase:	1
Brief Title: Phase 1 Study to Estimate the Effect of ARV-471 on Rosuvastatin Pharmacokinetics in Healthy Participants	

Document History

Document	Version Date
Original protocol	04 November 2022

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Interventional, Phase 1, Open-Label, Fixed-Sequence, 2-Period Study to Evaluate the Effect of A Single Oral Dose of ARV-471 (PF-07850327) on the Pharmacokinetics of Rosuvastatin in Healthy Participants

Brief Title: Phase 1 Study to Estimate the Effect of ARV-471 on Rosuvastatin Pharmacokinetics in Healthy Participants

Regulatory Agency Identification Number(s):

US IND Number:	CCI
EudraCT/CTIS Number:	Not applicable
ClinicalTrials.gov ID:	Not applicable
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C4891029
Phase:	1

Rationale:

In vitro, ARV-471 is a BCRP inhibitor. Although ARV-471 does not show inhibition against human BCRP in a CCI assay format up to the maximum soluble concentration of CCI it shows CCI inhibition against BCRP in a CCI assay format at the maximum soluble concentration of CCI The difference between the 2 assay formats is likely due to the CCI of ARV-471 in the bidirectional monolayer.

Assuming full solubility of the administered dose in the stomach, the maximum possible concentration of ARV-471 in the GI tract after an oral single dose of 200 mg ARV-471 would be 0.8 mg/mL (CCI assuming a gastric fluid volume of 250 mL) that is approximately CCI higher than CCI While in vitro risk assessment for CCI CCI can be CCI for drugs that have poor solubility (BCS Class II or IV), in vivo potential for ARV-471 to inhibit BCRP activity in human GI tract cannot be excluded.

Rosuvastatin is a prototypical substrate of BCRP. Administration of rosuvastatin with ARV-471 may lead to increased systemic exposure of rosuvastatin. The objective of this study is to estimate the effect of ARV-471 on the PK of rosuvastatin in healthy participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of a single oral 200 mg dose of ARV-471 on a single dose PK of rosuvastatin in healthy participants.	• Plasma rosuvastatin C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated)
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of rosuvastatin alone and following co-administration with a single oral dose of ARV-471.	• TEAEs, clinical laboratory tests, vital signs, PE, and ECGs
Other:	**Other:**
• To characterize the CCI of ARV-471 and its epimer, ARV-473, after a single oral 200 mg dose of ARV-471	• CCI as data permit and as appropriate
	• Other rosuvastatin PK parameters: plasma C_{last}, AUC_{last}, T_{max}, T_{last}, $t_{1/2}$, CL/F, V_z/F, as data permit

Overall Design:

This will be a Phase 1, open-label, 2-period, fixed-sequence study to estimate the effect of a single oral dose of ARV-471 on the PK of rosuvastatin under fed condition in healthy male participants and healthy female participants of non-childbearing potential. An attempt will be made to enroll more than 50% participants as female participants with non-childbearing potential in this study since ARV-471 is being developed for treatment in a population that is predominately female.

Number of Participants:

A sufficient number of participants will be screened to ensure that at least 12 participants will be enrolled in the study.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

1. Male and/or female participants of non-childbearing potential must be 18 to 65 years of age, inclusive at the time of signing ICD.

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

3. BMI of 17.5 to 32 kg/m^2; and a total body weight ≥45 kg.

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

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

Exclusion Criteria

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

2. Pregnant female participants; breastfeeding female participants; Male participants with partners currently pregnant; fertile male participants who have partners of childbearing potential and are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 90 days after the last dose of investigational product.

3. Participants with known history of hypersensitivity to statin medication, sensitivity to ARV-471 or rosuvastatin or any of the formulation components of ARV-471 or rosuvastatin.

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

5. Use of prescription or nonprescription medications, including vitamins, dietary and herbal supplements, within 7 days or 5 half-lives (whichever is longer) prior to the

first dose of study intervention. Additionally, a longer washout is required for the medications below:

- Moderate or strong CYP3A/BCRP inducers which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.
- Moderate or strong CYP3A/BCRP inhibitors which are prohibited within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention.

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

7. A positive urine drug test.

8. Screening supine BP ≥140 mm Hg (systolic) when age <60 years, ≥150 mm Hg (systolic) when age ≥60 years, or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) when age <60 years, ≥150 mm Hg (systolic) when age ≥60 years, or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

9. 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.

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

    - AST **or** ALT level >ULN;
    - Total bilirubin level >ULN;
    - Renal impairment as defined by an eGFR in adults of ≤60 mL/min/1.73m^2.
    - Hypothyroidism

11. History of use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day.

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

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

14. Unwilling or unable to comply with lifestyle requirements described in this protocol.

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

Study Arms and Duration:

The fixed sequence study will consist of 2 periods: Period 1 = single oral dose of rosuvastatin alone; Period 2 = single oral dose of ARV-471 + single oral dose of rosuvastatin with staggered dosing times. A washout of at least 5 days must occur between the 2 successive single doses of rosuvastatin. Following administration of rosuvastatin in each period, participants will undergo serial PK sampling.

Study Intervention(s)		
Intervention Name	ARV-471 (PF-07850327)	Rosuvastatin (CRESTOR®)
Arm Name (group of participants receiving a specific treatment or no treatment)	Period 2 only	Periods 1 and 2
Unit Dose Strength(s)	100 mg	10 mg
Route of Administration	Oral	Oral
Use	Experimental	Experimental treatment to assess as probe substrate in current DDI study
IMP or NIMP/AxMP	IMP	NIMP/AxMP

Statistical Methods:

A sufficient number of participants will be screened to ensure that at least 12 participants will be enrolled in the study. The sample size is empirically selected and is not based on statistical power calculation. A sample size of 12 PK evaluable participants who have at least 1 of the rosuvastatin PK parameters of primary interest (AUC_{inf} or C_{max}) is expected to provide 90%

CIs for the difference between treatments of [redacted] and [redacted] on the natural log scale for AUC_{inf} and C_{max}, respectively, with 80% coverage probability.

The plasma concentrations of rosuvastatin 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 period for each analyte 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. For comparison of rosuvastatin AUC_{inf} and C_{max} with and without ARV-471, box and whisker plots of these parameters will be plotted by period.

Natural log transformed parameters (AUC_{inf} [if data permit)], AUC_{last}, and C_{max}) of rosuvastatin will be analyzed using a mixed effect model with treatment as fixed effects and participant 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. Rosuvastatin administered alone will be the reference treatment and ARV-471 co-administered with rosuvastatin will be the test treatment.

Ethical Considerations:

Neither ARV-471 nor rosuvastatin will provide clinical benefit to healthy participants in this study. Any anticipated benefit to participants would be in terms of contribution to the process of developing a new therapy in an area of unmet medical need.

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.

Table 1. Period 1 (Rosuvastatin) and Period 2 (Rosuvastatin with ARV-471)

Visit Identifier Abbreviations used in this table may be found in Appendix 9	**Screen**	**Period 1**						**Period 2**				**Follow -Up**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**28-35 Days**		• All screening should be done ≤28 days before the first dose of study intervention. • Day relative to start of study intervention (Day 1). • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Informed consent	X													• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
CRU confinement		X	→	→	→	→	→	→	→	→	X			• Participants will be admitted to the CRU on the day prior to Period 1 dosing (Day -1). Participants will be discharged on Period 2 Day 4 following PK sampling.
Inclusion/exclusion criteria	X	X												• See Sections 5.1 and 5.2 for details

Table 1. Period 1 (Rosuvastatin) and Period 2 (Rosuvastatin with ARV-471)

Visit Identifier Abbreviations used in this table may be found in Appendix 9	**Screen**	**Period 1**						**Period 2**				**Follow -Up**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**28-35 Days**		• All screening should be done ≤28 days before the first dose of study intervention. • Day relative to start of study intervention (Day 1). • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Medical/medication history	X	X												• Medical history will include a history of prior illegal drug, alcohol, and tobacco use. Medical history will be recorded at Screening and updated on Day -1 of Period 1 only.
Physical exam	X	X												• A complete exam, without genitourinary evaluation will be performed by trained medical personnel at the investigator site at Screening or Day -1 of Period 1 only (height and weight must be obtained at Screening to obtain BMI for eligibility criteria). A limited PE may be performed at other designated time points at the discretion of the investigator. Only weight needs to be recorded thereafter. • See Section 8.3.1 for details.

Table 1. Period 1 (Rosuvastatin) and Period 2 (Rosuvastatin with ARV-471)

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Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**28-35 Days**		• All screening should be done ≤28 days before the first dose of study intervention. • Day relative to start of study intervention (Day 1). • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Safety laboratory	X	X					X				X		X	• Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed at the indicated time-points. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator. See Section 8.3.4 and Appendix 2 for details. • Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.
Demography	X													• Demographics will include participant, race, ethnicity, age, and gender during the screening visit.
Contraception check	X	X									X	X	X	• On Screening and Day -1, the investigator or his/her designee will discuss with male participants the need to use highly effective contraception consistently and correctly according to contraception guidelines.
FSH	X													• For postmenopausal (amenorrheic for at least 12 consecutive months) female participants only.
TSH	X													

Table 1. Period 1 (Rosuvastatin) and Period 2 (Rosuvastatin with ARV-471)

Visit Identifier Abbreviations used in this table may be found in Appendix 9	**Screen**	**Period 1**						**Period 2**				**Follow -Up**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**28-35 Days**		• All screening should be done ≤28 days before the first dose of study intervention. • Day relative to start of study intervention (Day 1). • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Urine drug testing	X	X												• Urine drug (mandatory) and alcohol breath test (at discretion of investigator) will be performed at Screening and on Day -1. These tests may be performed at any other time at the discretion of the investigator.
12-Lead ECG	X		X					X			X		X	• Refer to Table 2and Table 3for 12-lead ECG collections.
Vital signs (BP/PR)	X		X					X			X		X	• Refer to Table 2and Table 3for the specified timepoints.
Serology: HIV, HBsAg, HBsAb, HBcAb, HCVAb	X													• HBsAb may be routinely tested or only if HBsAg and/or HBcAb are positive. HBsAb due to vaccination is permissible
COVID-19 related measures	X	X	X	X	X	X	X	X	X	X	X			• Performed per local procedures
Rosuvastatin administration			X					X						• Refer to Table 2and Table 3for the specified timepoints. • Refer to Section 6.1.1 for details of administration requirement.
ARV-471 administration								X						• Refer to Table 3for the specified timepoint. • Refer to Section 6.1.1 for details of administration requirement.

Table 1. Period 1 (Rosuvastatin) and Period 2 (Rosuvastatin with ARV-471)

Visit Identifier Abbreviations used in this table may be found in Appendix 9	**Screen**	**Period 1**						**Period 2**				**Follow -Up**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**28-35 Days**		• All screening should be done ≤28 days before the first dose of study intervention. • Day relative to start of study intervention (Day 1). • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Pharmacokinetic blood sampling			X	X	X	X		X	X	X	X		X	• Please refer to Table 2and Table 3for detailed PK sampling schedule in each period.
Retained Research Sample for Genetics (Prep D1)			X											• Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. See Section 8.6.2.
CRU discharge											X			• Follow-up visit activities (if necessary) will be performed at the discretion of the principal investigator, if there is an unresolved AE at discharge, or in the case of an early discontinuation.
Serious and non-serious AE monitoring	X	→	→	→	→	→	→	→	→	→	X	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Prior/Concomitant Treatment Assessment	X	X										X		• Refer to Section 5.2 and Section 6.9 for details.

Table 2. Period 1 (Single Oral Dose of Rosuvastatin): PK and ECG Sampling Schedule

Visit Identifier Abbreviations used in this table maybe found in Appendix 9	**Period 1 (Single oral dose of rosuvastatin)**												**Notes**
Study Day	**Day 1**								**Day 2**		**Day 3**	**Day 4**	
Hours Before/After Dose	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	Hour 0 = predose sample collection
Rosuvastatin administration	X												• Refer to Section 6.1.1 for details of administration requirement.
Rosuvastatin PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	• Refer to Section 8.5 for additional details.
12-Lead ECG	X (triplicate)												• Triplicate ECG will be collected for baseline measurement at pre-dose. 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 measurement. • See Section 8.3.3 for details.
Vital signs (BP/PR)	X												• Single supine blood pressure and pulse rate will be performed following at least a 5-minute rest in a supine position. BP and PR assessment will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. • See Section 8.3.2 for details.

Table 3. Period 2 (Single Oral Dose of Rosuvastatin with ARV-471): PK and ECG Sampling Schedule

Visit Identifier Abbreviations used in this table maybe found in Appendix 9	**Period 2 (Single oral dose of rosuvastatin with single oral dose of ARV-471)**														**Notes**
Study Day	**Day 1**										**Day 2**		**Day 3**	**Day 4**	
Hours Before/After Dose	**-1.5**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	Hour 0 = predose sample collection
ARV-471 administration	X														• Refer to Section 6.1.1 for details of administration requirement.
Rosuvastatin administration		X													• Refer to Section 6.1.1 for details of administration requirement.
Rosuvastatin PK blood sampling		X		X	X	X	X	X	X	X	X	X	X	X	• Refer to Section 8.5 for additional details.
CCI [redacted]	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-Lead ECG	X						X							X	• Singlet ECG will be taken at specific timepoints. 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 measurement. • See Section 8.3.3 for details.
Vital signs (BP/PR)	X						X							X	• Single supine blood pressure and pulse rate will be performed following at least a 5-minute rest in a supine position. BP and PR assessment will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. • See Section 8.3.2 for details.

2. INTRODUCTION

ARV-471 (PF-07850327) is a potent, selective, orally bioavailable PROTAC® small molecule that induces degradation of the ER. ARV-471 is being developed for the treatment of patients with ER+/HER2- mBC.

2.1. Study Rationale

ARV-471 is a BCS Class IV compound (low solubility/low permeability). ARV-471 does not show inhibition against human BCRP on a CCI assay up to the maximum soluble concentration of CCI while showing CCI inhibition against BCRP in a CCI assay at the maximum soluble concentration of CCI The difference between the 2 assays is likely due to the CCI of ARV-471 in the bidirectional monolayer. Taken together, in vitro, ARV-471 is a BCRP inhibitor.

Assuming full solubility of the administered dose in the stomach, the maximum possible concentration of ARV-471 in the GI tract after a single dose of 200 mg ARV-471 would be 0.8 mg/mL CCI assuming a gastric fluid volume of 250 mL) that is approximately CCI than CCI While in vitro risk assessment for CCI can be CCI for drugs that have poor solubility (BCS Class II or IV), in vivo potential for ARV-471 to inhibit BCRP activity in human GI tract cannot be excluded. Therefore, a clinical interaction study with BCRP substrate is needed to assess the effect of ARV-471 on exposures of BCRP substrates.

Rosuvastatin is a prototypical substrate of BCRP[1,2]. Administration of rosuvastatin with ARV-471 may lead to increased systemic exposure of rosuvastatin. The objective of this study is to estimate the effect of ARV-471 on the PK of rosuvastatin in healthy participants.

2.2. Background

ARV-471 (PF-07850327) is a potent, selective, orally bioavailable PROTAC® small molecule that induces degradation of the ER. ARV-471 is a hetero-bifunctional PROTAC® molecule that simultaneously binds the ER and the cereblon E3 ligase complex, enabling protein-protein interactions between ER and the ligase complex. As a result, the ER becomes poly-ubiquitinated on accessible lysine residues and subsequently undergoes targeted degradation by the proteasome to affect its elimination from cells.

2.2.1. Nonclinical Pharmacology

In a panel of ER+ cell lines, ARV-471 treatment resulted in a CCI reduction in ER levels, similar to those observed with fulvestrant. In CCI cells, ARV-471 achieved a DC_{50} of CCI with a maximum ER degradation of CCI In addition to ARV-471, its epimer, ARV-473, was assessed for ER degradation activity. While both ARV-471 and fulvestrant reduced ER levels, ARV-473 CCI ER levels, even when tested at 1 µM. In an ER dependent gene reporter assay, ARV-471 and ARV-473 had similar CCI activity, indicating that ARV-471 has both CCI and degradation activities against ER, whereas ARV-473 displays only CCI activity.

ARV-471 decreased levels of clinically relevant ER CCI mutations in a CCI manner similar to fulvestrant. In the same study, ARV-471 inhibited growth of these CCI cell lines with GI_{50} values of CCI and 8 nM for ERCCI and ER CCI respectively. Taken together, ARV-471 demonstrates both ER degradation and anti-proliferative activity in cells expressing the most prevalent ER mutations.

ARV-471 demonstrates superior TGI compared to fulvestrant in a Y537S ESR1 mutant patient-derived xenograft model. In the MCF7-xenograft mouse model, 3 to 30 mg/kg ARV-471, orally administered to mice once daily for 28 days, displayed dose-dependent efficacy with doses of 3 and 10 mg/kg/day inhibiting tumor growth by 85% and 98%, respectively and 30 mg/kg/day leading to tumor shrinkage (124% TGI). At study termination, the tumor ER levels were reduced by ≥94%, suggesting that higher doses are required for maximal efficacy than for maximal ER degradation.

These nonclinical data suggest that ARV-471 has the potential to offer improved ER degradation as compared to fulvestrant.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

ARV-471 is a BCS Class IV compound (low solubility/low permeability). The PK profile of ARV-471 in the preclinical species (mouse, rat, dog, and monkey) was characterized by a CCI clearance CCI to CCI of hepatic blood flow), CCI tissue distribution (CCI to CCI CCI to CCI $t_{1/2}$ CCI to CCI hours), and CCI to CCI oral bioavailability (27% to 65%).

ARV-471 can interconvert to its epimer, ARV-473. Plasma exposure of ARV-473 relative to ARV-471 upon ARV-471 dosing was CCI in animal PK and TK studies (CCI). ARV-473 does not CCI the ER, however, ARV-473 showed similar CCI of ER-dependent transcription compared to ARV-471.

A CYP reaction phenotyping study was conducted using two orthogonal methods in human liver microsomes and recombinant CYP isoforms that are consistent with current FDA guidance[3]. This study indicated that CYP3A4 as the principal isoform responsible for CYP metabolism of ARV-471 (accounting for 85%).

Based on in vitro studies, ARV-471 is not a substrate for P-gp, BCRP, OATP1B1, and OATP1B3.

ARV-471 at concentrations up to 24 µM had no or limited direct inhibition against CYP1A2, 2C8, 2C9, 2C19, 2D6, and 3A4 (with either midazolam or testosterone as the probe substrate), indicating IC_{50} >24 µM. ARV-471 inhibited CYP2B6 with an IC_{50} of 16.0 µM. There was no evidence for mechanism-based inhibition against any of the CYP isoforms in the same study. Mechanistic static modeling, using bupropion as the probe CYP2B6 substrate drug, indicated a low potential for DDI due to ARV-471-mediated reversible inhibition of CYP2B6 at human exposures associated with the 500 mg QD ARV-471 dose.

In a separate study, ARV-473 at concentrations of up to 24 µM had no or limited direct inhibition against CYP 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4 (with either midazolam or testosterone as the probe substrate), indicating IC_{50} >24 µM. ARV-473 inhibited CYP2B6 activity with an apparent IC_{50} value of 23.4 µM. There was no evidence for mechanism-based inhibition against any of the aforementioned CYP isoforms in the same study.

Enzyme induction studies in human hepatocytes indicated that ARV-471 is not an in vitro inducer of CYP1A2, 2B6, and 3A4.

ARV-471 does not show inhibition against human BCRP on a CCI CCI assay format up to the maximum soluble concentration of CCI while showing CCI inhibition against BCRP in a CCI assay format at the maximum soluble concentration of CCI The difference between the two assay formats is likely due to the CCI of ARV-471 in the bidirectional monolayer. Similarly, ARV-471 does not show inhibition against P-gp on a CCI assay format up to the maximum soluble concentration of CCI while showing an IC_{50} of CCI in a CCI assay format. The difference between the two assay formats is likely due to the CCI CCI of ARV-471 in the bidirectional monolayer.

ARV-471 showed no or minimum inhibition against OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K when tested at the maximum solubility of 2.5 µM in the test media.

A dose-dependent increase in ARV-471 exposure was observed when ARV-471 was administered as an oral solution in the mouse (10, 30, 100 mg/kg), rat (30, 100, 300 mg/kg), dog (15, 45, 90, 200, 400 mg/kg), and monkey (1 and 3 mg/kg).

A 3-fold increase in AUC and reduced inter-animal variability was observed in fed dogs; as such, the data indicated that the tablets should be administered with food in clinical trials.

Refer to ARV-471 (PF-07850327) IB for additional information.

2.2.3. Nonclinical Safety

A high-level review of key nonclinical safety data is summarized below, additional information can be found in the IB.

The potential for ARV-471 and ARV-473 to impact the cardiovascular system was assessed in vitro and in single- and repeat-dose in vivo studies. Neither compound directly CCI the CCI ; however, CCI in the CCI were noted after CCI (but not 1-month) ARV-471 administration in dogs. Changes in the CCI were only observed after CCI No indication of CCI were observed in any study. There were no significant respiratory or CNS effects. ARV-471 and ARV-473 did not impact CCI CCI was initially assessed at the nominal concentration of CCI and CCI CCI respectively.

In a dedicated GLP cardiovascular assessment, a single dose of ARV-471 was administered via oral gavage to telemetered conscious male and female beagle dogs at doses of CCI and CCI No ARV-471-related effects were noted after oral administration of ARV-471 at CCI and CCI . Following administration of ARV-471 at CCI a statistically significant 7 ms CCI of the CCI was noted from 1 to CCI postdose. No other ARV-471 related effects were noted at CCI At CCI (the only dose studied in the TK phase), dogs (n=8, males and females combined) achieved a mean of CCI for C_{max}, CCI for T_{max}, and CCI for AUC_{0-24}.

Nonclinical toxicology studies were conducted with ARV-471 to evaluate the potential toxicity and determine the TK profile of ARV-471 and its epimer ARV-473 when administered once daily orally (by gavage). The toxicology program includes up to 3-month GLP compliant repeat-dose studies in rats and dogs, GLP-compliant in vitro bacterial reverse mutation (Ames) assay, GLP-compliant in vitro micronucleus assay, and a GLP-compliant in vitro 3T3 phototoxicity study.

ARV-471 was CCI in repeat dose rat studies up to 3-months in duration at doses up CCI . ARV-471-related CCI were considered related to the CCI and included CCI in females administered CCI and CCI and of the CCI and CCI in females administered CCI The CCI in the CCI CCI were CCI and considered to be due to the CCI of ARV-471. The CCI of CCI (compared to controls) of CCI CCI were CCI or CCI relationship and were not associated with changes to the CCI , and no other CCI changes were observed. Notably, however, a subsequent 3-month study in rats showed there were no findings in the CCI , suggesting these were spurious findings in the 28-day study. The NOAEL for daily oral administration of ARV-471 to rats for 28 days was determined to be CCI . ARV-471 was CCI following once-daily oral (by gavage) dosing in the GLP compliant 3-month toxicity study in rats up to CCI The NOAEL for 3 months of oral dosing was determined to be the highest dose tested of CCI in male rats. A NOAEL was not identified in female rats as the effects on the reproductive tract were consider adverse. However, these findings are related to the primary pharmacology of ARV-471, reversible and not anticipated after short duration dosing. At the CCI dose level, the C_{max} was CCI and CCI in males and females, respectively, and the AUC_{0-24} was CCI and CCI in males and females, respectively.

ARV-471 was well tolerated in repeat dose dog studies up to 3-months in duration at doses up CCI . There were CCI and no ARV-471-related CCI changes in CCI or CCI or CCI . There were no ARV-471-related CCI observed, including no effects on CCI CCI , or CCI and CCI or CCI in the 1-month study.

ARV-471 produced changes in female and male reproductive tissues, consistent with pharmacological effects of the drug. In females, there were findings in the CCI and in the CCI CCI these findings were considered adverse. In males, findings in the CCI and CCI were considered non-adverse. Additional, non-adverse findings attributed to ARV-471 were noted in the CCI CCI and in the CCI The 90 mg/kg/day was identified as the NOAEL for daily dosing for 3 months in males. A NOAEL was not identified for females based upon CCI in the CCI CCI that were considered adverse, but it is acknowledged that these effects were consistent with the pharmacological effects of ARV-471, expected to be reversible. In males at CCI the C_{max} was CCI and AUC_{0-24} was CCI on Day 91. At the low dose (CCI for females, the associated C_{max} was CCI, and AUC_{0-24} was CCI on Day 91.

2.2.4. Clinical Overview

In the ongoing FIH study, Study ARV-471-mBC-101, ARV-471 is being assessed as a monotherapy and in combination with palbociclib in patients with advanced/metastatic ER+/HER2- BC. The FIH study has 3 parts: Part A is a monotherapy dose escalation, Part B is a monotherapy expansion at two RP2Ds (200 mg QD, 500 mg QD), and Part C is evaluating the combination of ARV-471 and palbociclib. As of 06 Jun 2022, 176 participants have been treated in the FIH study (Part A, n=78; Part B, n=71; Part C, n=27).

In study ARV-471-mBC-101 to date, monotherapy ARV-471 has demonstrated to be well-tolerated across total daily doses of 30 mg to 700 mg in patients with mBC. No DLTs were observed and majority of TRAEs in Part A were Grade 1 CCI) or 2 (CCI) and manageable. In addition, palbociclib in combination with ARV-471 shows a safety profile similar to that of palbociclib alone or palbociclib in combination with endocrine therapy. As of 06 June 2022, 13 patients in the Phase 1/2 study, Study ARV-471-mBC-101, have received the sensitive BCRP substrate rosuvastatin (1 patient received 2.5 mg daily, 5 patients received 5 mg daily, 3 patients received 10 mg daily, 3 patients received 20 mg daily, and 1 patient had an unknown dose) with no changes in overall safety profiles. There were no reports of CCI in these patients, and 1 patient reported CCI CCI Three patients had CCI reported, which included CCI each of CCI All of these events were not related to ARV-471, except for 1 patient with CCI that was attributable to CCI. One additional patient with reported CCI CCI also had a CCI both events deemed related to CCI

The ongoing Phase 1 clinical pharmacology study, CCI, is evaluating the effect of food or a PPI and the relative bioavailability of different tablet formulations on the single-dose PK and safety of ARV-471 in healthy postmenopausal female participants.

A single oral dose of 200 mg ARV-471 has been well-tolerated in healthy participants, and no TRAEs of Grade 2 or higher were reported in the study.

Preliminary PK data from Study CCI (as of 06 Jun 2022) showed dose-dependent increases in Cycle 1 Day 15 AUC_{0-24} that were observed up to daily doses of 500 mg. Doses above 60 mg QD achieved average AUC_{0-24} that exceeded the nonclinical exposure (AUC_{inf}=CCI at 30 mg/kg, single dose) associated with tumor shrinkage in MCF7-tumor-bearing NOD/scid mice.

Analysis of 14 paired biopsies from Part A suggested robust ER degradation (median decrease = CCI [range: CCI to CCI]), in patients with WT or mutant ER. Furthermore, there was evidence of preliminary clinical activity in the monotherapy dose escalation, with several patients achieving clinical benefit (by CBR).

The results from these nonclinical pharmacology, PK and metabolism, and toxicology studies and available clinical safety and efficacy data support continued clinical development of ARV-471 in ER+/HER2- advanced breast cancer.

Please refer to ARV-471 (PF-07850327) IB for additional information.

2.2.4.1. Summary of ARV-471 Pharmacokinetics in Humans

Preliminary PK data from Part A monotherapy dose escalation of Study CCI (as of 06 Jun 2022) are available from dose levels ranging from 30 to 700 mg administered either as QD or BID. Preliminary results indicated dose-dependent increases in C_{max} and AUC_{tau} for ARV-471, ARV-473, and sum of ARV-471 and ARV-473 up to 500 mg total daily dose administered either as 250 mg BID or 500 mg QD on both Cycle 1 Day 1 and Day 15. The median T_{max} ranged from CCI across the dose levels. The mean effective $t_{1/2}$ at steady state ranged from CCI

Following 200 mg QD dosing, a geometric mean accumulation ratio based on AUC_{tau} of CCI was observed between Day 1 and Day 15. The ratio of ARV-473/ARV-471 based on AUC_{tau}, on Cycle 1 Day 15 is CCI

CCI is a Phase 1, multi-part, open-label study to evaluate the effect of food or a PPI and to evaluate the relative bioavailability of different tablet formulations on the single 200 mg dose pharmacokinetics and safety of ARV-471 in healthy post-menopausal female participants. The median T_{max} ranged from CCI hours across the cohorts. The geometric mean $t_{1/2}$ following a single oral 200 mg dose was approximately CCI under fed condition. Food intake increased ARV-471 C_{max} for CCI and AUC_{inf} for CCI as compared with fasted conditions. Data indicated CCI on exposure of ARV-471 when administered with a CCI. Exposures of ARV-471 (C_{max} and AUC) of CCI drug-loaded SDD tablets (tests) were similar to the CCI drug-loaded SDD tablets (reference) when administered with a moderate-fat meal.

Please refer to ARV-471 (PF-07850327) IB for additional information.

2.3. Benefit/Risk Assessment

Neither ARV-471 nor rosuvastatin are expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ARV-471 may be found in the IB, which is the SRSD for this study. The SRSD for the rosuvastatin is the USPI of Crestor®.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Study Intervention(s) ARV-471	
CCI	CCI based on CCI to date as per Section 2.2.3. CCI modeling analysis revealed a CCI in CCI Thirteen participants were reported with CCI in the ongoing FIH study CCI), for 12 participants the event was considered related. An external CCI consultant review concluded that 2 participants had a true diagnosis of CCI, of which CCI and CCI were confounding factors. Clinical safety is not yet fully quantified.	Participants will receive a single 200 mg dose of ARV-471 in Period 2. The C_{max} of ARV-471 after a single 200 mg is expected to be less than that after repeated dosing at 200 mg in participants with mBC from Study CCI Based on the CCI, the CCI was predicted to be CCI at the geometric mean C_{max} of CCI ng/mL after a single dose of 200 mg ARV-471 in healthy post-menopausal female[b]. Participants will be monitored for CCI changes with CCI at screening, Period 1 pre-dose and at additional time points during Period 2. Participants with clinically relevant abnormalities demonstrated in the standard CCI will be excluded (Section 5.2). Use of prescription or nonprescription drugs including dietary and herbal supplements, vitamins, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products are prohibited in this study.
CCI	Potential risk based on metastatic cancer setting and known class effect with CCI One Grade 3 related CCI, with confounding factors of obesity, diabetes and immobile due to recent procedure and a Grade 3 serious CCI case assessed as unlikely related to ARV-471 by the investigator, were reported from the ongoing FIH study CCI	Participants will receive a single 200 mg dose of ARV-471 in Period 2. Participants with a history of clinically significant CCI events are excluded from participation in the study as per EC #1 (see Section 5.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Rosuvastatin		
Skeletal muscle effects (eg, myopathy and rhabdomyolysis)	Risks increase with use of 40 mg dose, advanced age (≥65), hypothyroidism, renal impairment, and combination use with cyclosporine, darolutamide, regorafenib, certain anti-viral medicines or their combinations. Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported.	Single rosuvastatin dose of 10 mg is administered in the study and poses minimal risk. Participants with advanced age, renal impairment or hypothyroidism are not included from participation in the study as per IC #1 and EC #10 (see Section 5.1 and Section 5.2).
IMNM	There have been rare reports of IMNM, an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents	Participants with known history of hypersensitivity to statin use are excluded from participation in the study as per EC #3 (see Section 5.2).
Liver enzyme abnormalities	Persistent elevations in hepatic transaminases can occur.	Single rosuvastatin dose of 10 mg is administered in the study and poses minimal risk. Instructions for managing potential cases of drug-induced liver injury, should they occur, are provided in Appendix 6.

a. CCI Table 11, ARV-471 CCI estimate (90% CI): CCI.
b. Study CCI CSR Table 14.2.2.3.

2.3.2. Benefit Assessment

Neither ARV-471 nor rosuvastatin will provide any clinical benefit to healthy participants in this study. Any anticipated benefit to participants would be in terms of contribution to the process of developing a new therapy in an area of unmet medical need.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with ARV-471 and/or rosuvastatin are justified by the anticipated benefits that may be afforded to future study participants with ER+ and HER2- mBC.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of a single oral 200 mg dose of ARV-471 on a single dose PK of rosuvastatin in healthy participants.	• Plasma rosuvastatin C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated)
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of rosuvastatin alone and following co-administration with a single oral dose of ARV-471.	• TEAEs, clinical laboratory tests, vital signs, PE, and ECGs
Other:	**Other:**
• To characterize the CCI of ARV-471 and its epimer, ARV-473 after a single oral 200 mg dose of ARV-471.	• CCI as data permit and as appropriate
	• Rosuvastatin PK parameters: plasma C_{last}, AUC_{last}, T_{max}, T_{last}, $t_{1/2}$, CL/F, V_z/F, as data permit

4. STUDY DESIGN

4.1. Overall Design

This will be a Phase 1, open-label, 2-period, fixed-sequence study, estimating the effect of a single oral dose of ARV-471 on the PK of a BCRP substrate, rosuvastatin, in healthy male participants and healthy female participants of non-childbearing potential. An attempt will be made to enroll more than 50% participants as female participants with non-childbearing potential in this study since ARV-471 is being developed for the treatment of mBC.

This study will consistent of 2 Periods. In Period 1, a standard breakfast will be provided approximately 2 hours (120 minutes) prior to rosuvastatin single dose (10 mg) administration on Day 1. The breakfast will be required to be completely consumed within an approximately 20-minute period. To avoid rosuvastatin effects from the previous period, a minimum washout period of 5 days will be required after rosuvastatin administration on Period 1 Day 1.

In Period 2, a standard breakfast will be provided approximately 30 minutes prior to ARV-471 single dose (200 mg) on Day 1. The breakfast will be required to be completely consumed within an approximately 20-minute period. A single dose of 10 mg rosuvastatin will be administered approximately 1.5 hour (90 minutes) after ARV-471 dosing, which will be approximately 2 hours (120 minutes) after the start of the breakfast.

Serial PK samples will be collected up to 72 hours following administration of rosuvastatin in each period to estimate the single dose PK parameters of rosuvastatin.

A sufficient number of participants will be screened to ensure that at least 12 participants will be enrolled in the study. Participants who withdraw may be replaced at the discretion of the sponsor. Healthy participants will be screened to determine eligibility within 28 days prior to study treatment (ie, within 28 days prior to Day 1 of Period 1).

Participants will be admitted to the CRU on Day -1 and will be required to remain in the CRU for 10 days and 9 nights. Washout period will begin after the first dose of study intervention.

ARV-471 (PF-07850327) will be supplied by Pfizer. Rosuvastatin (CRESTOR®) as 10 mg tablets will be sourced locally by the CRU.

The total planned duration of participation, from Screening visit to the last follow-up phone call, is approximately 10 weeks.

Safety assessments will be performed during Screening, on Day -1 prior to dosing, and at specified time points in SoA. PEs, vital sign measurements, and clinical laboratory tests will be conducted, and AEs will be monitored to assess safety. The total participation time (eg, CRU confinement time for study procedures) for each participant in this study is approximately 10 days/9 nights (excluding screening and follow-up contact).

4.2. Scientific Rationale for Study Design

4.2.1. Probe Substrate Selection

Rosuvastatin is a probe substrate for both intestinal and hepatic BCRP. Intestinal BCRP acts as an efflux transporter limiting rosuvastatin absorption, while liver BCRP actively excretes rosuvastatin into the bile[1]. Rosuvastatin is also a substrate for OATP1B and OAT3. However, ARV-471 is CCI [redacted] as ARV-471 is CCI [redacted] Hence, potential inhibition of BCRP by ARV-471 would be expected to increase rosuvastatin plasma exposure, which will be assessed as the primary endpoint of the current study. The plasma terminal elimination half-life of rosuvastatin is approximately 19 hours[4]. Therefore, plasma PK samples for rosuvastatin will be collected up to 72 hours post-dosing to ensure that the majority of rosuvastatin is characterized. This is also the reason for the minimum 5-day washout period between the 2 consecutive rosuvastatin doses in this study.

4.2.2. Administration of Study Drugs With Food

CCI is a Phase 1, multi-part, open-label study to evaluate the effect of food or a PPI and to evaluate the relative bioavailability of different tablet formulations on the single 200 mg dose pharmacokinetics and safety of ARV-471 in healthy participants.

Preliminary results from that study indicate that CCI ARV-471 C_{max} for CCI and AUC_{inf} for CCI as compared with CCI condition. Cross cohort comparison showed similar or higher ARV-471 plasma exposures with a CCI (approximately CCI calories with a fat content of approximately CCI) meal versus a CCI meal (approximately CCI calories, consisting of at least CCI calories from protein, CCI calories from carbohydrates and CCI calories from fat) with the prior formulation CCI DL with CCI SDD). ARV-471 is recommended to be CCI for clinical studies. The new formulation CCI DL with CCI SDD) showed similar exposure compared with the prior formulation (CCI DL with CCI SDD). The median T_{max} was CCI hours and the $t_{1/2}$ of ARV-471 after a single 200 mg dose was approximately CCI hours.

Considering the data available to date and the intended formulation to be used in this study (CCI DL with CCI SDD), ARV-471 will be administered with a CCI breakfast (approximately CCI calories with a fat content of approximately CCI) to CCI

4.2.3. Inclusion of Females of Non-childbearing Potential

ARV-471 is known to cause CCI in the CCI CCI of female rats and dogs and male dogs, which may be regarded as CCI CCI and which are considered related to the CCI of ARV-471. Therefore, there is a CCI of CCI. Studies to evaluate the CCI of ARV-471 in CCI However, based on its CCI, ARV-471 may cause CCI when administered to CCI CCI therefore CCI.

4.2.4. Inclusion of Male Participants

Nonclinical toxicology studies are reviewed in Section 2.2.3 and the most recent IB is included for reference.

The repeat dose CCI studies in rats and dogs have consistently shown ARV-471 to be CCI after once-daily dosing. The 3-month studies have shown CCI of CCI and CCI and CCI of the animals following daily oral doses of ARV-471 up to CCI in rats and CCI in dogs. Across the studies, there were CCI, or CCI

In all studies, the pharmacologic effects of ARV-471 were on the CCI CCI in the toxicology studies in both rat and dog are known to express both ERa and ERb. Findings in the CCI

CCI and, at low doses, CCI are consistent with the CCI of ARV-471 on the ER and have been observed for agents that target the ER (eg, fulvestrant).

Findings in CCI were only observed in the dog and CCI were noted in the rat in studies up to 3-month in duration. In the 28-day toxicity study ARV-471-related CCI effects included CCI CCI CCI in animals administered CCI. A finding of CCI was ARV-471-related CCI in recovery sacrifice males included CCI CCI CCI of the CCI and CCI CCI which correlated with CCI, and CCI. These findings in CCI may have reflected the CCI CCI after degradation of the ER, compared to the CCI CCI A contributing factor to the effects on the CCI CCI in the 28-day toxicity studies is likely the male dog sexually maturity at the initiation of dosing (7-9 months old). The male specific findings were considered non-adverse and NOAEL of CCI was determined. In a follow-up 3-month (91-day) study the key findings in males consisted of CCI in the CCI of the CCI and CCI CCI with CCI. The CCI CCI in the 3-month toxicity study may be explained by the sexual maturity of the dogs at the initiation of dosing.

Table 4. Exposure Margin Determination for CCI in Rat and Dog Toxicity Studies

Species	Duration of ARV-471 administration	No effect or no adverse effect dose (mg/kg/day)	Male Total AUC_{24} (ng•h/mL)	Male Exposure Margin (200 mg clinical AUC)[a]	Male Exposure Margin (200 mg clinical AUC) HV[b]
Rat	7 days	300 (NOEL)	CCI		
Rat	28 days	100 (NOEL)	CCI		
Rat	91 days	300 (NOEL)	CCI		
Dog	7 days	120 (NOAEL)	CCI		
Dog	28 days	90 (NOAEL)	CCI		
Dog	91 days	90 (NOAEL)	CCI		

a. AUC_{tau} taken from IB Version 4.0 for 200 mg dose of ARV-471 of CCI in participants with mBC.
b. AUC_{inf} taken from preliminary data of CCI – test formulation arm CCI DL and CCI SDD) for a single 200 mg dose of ARV-471 of CCI in healthy participants.

In vitro CCI have been conducted with ARV-471 to CCI of studies in healthy participants and results are CCI

While a single dose of ARV-471 may carry CCI of producing CCI CCI on the CCI of ARV-471, the risk of CCI In the literature, a total of 21 drugs were administered at a single dose level and a single administration, to adult male mice, and groups of mice were euthanized and examined over

the course of 56 days[5,6]. Given the germ cell kinetics in the mouse testis, measuring testicular spermatid heads 56 days after treatment reflects the activity of the stem cell spermatogonia, and presumably the long-term spermatogenic activity of the testis thereafter. Using doses at or near the LD_{50}, most drugs gave modest or no detectable change at 56 days. Nineteen conventional chemotherapeutic drugs, given to mice as a single administration at or near the LD_{50}, caused no permanent sterility[5,6]. Only 2 out of 21 drugs tested (thiotepa and ADR) produced a permanent reduction >50% in testicular spermatid heads. In addition, Lu et al pointed out that "the effects of ADR in humans appeared to be less drastic than in mice. Two of 4 patients who received ≥400 mg/m^2 doses of ADR still possessed sperm counts of over 2 million"[5]. Meistrich et al also pointed out that these 2 drugs, thiotepa and adriamycin, are strong mutagens, CCI

In summary, given that the CCI tested provided a CCI of CCI in the 3-month toxicity study, the CCI to CCI in dogs shown in all studies to date, the CCI in the rat and also the profile in mice for the nongenotoxic drugs at doses around the LD_{50} in the literature, the risk of any CCI is assessed to be CCI when ARV-471 is administered as a single oral dose.

The current study will be conducted in healthy participants who will receive ARV-471 200 mg single dose alone in the fed state. Rosuvastatin is not an inhibitor or an inducer of CYP450 enzymes and is not expected to alter the metabolism of co-administered drugs that are substrate of CYP enzymes. As indicated above, for a single oral 200 mg dose the CCI CCI provides a safety margin of CCI with respect to the CCI in the 3-month toxicity study recommended by ICH Guidance[7].

4.2.5. Choice of Contraception/Barrier Requirements

ARV-471 is known to CCI in humans or suspected on the basis of CCI. Therefore, the use of a CCI CCI is required (see Appendix 4).

4.2.6. 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

A dose of 200 mg ARV-471 administered as a single oral dose will be used in this study. This is the current, proposed Phase 3 dose of ARV-471. A single oral dose of 10 mg rosuvastatin will be used in this study.

In participants with ER+/HER2- mBC, multiple daily doses up to 700 mg ARV-471 have been shown to be safe and well tolerated in patients with mBC. A single dose of 200 mg has been tested in a Phase 1, multi-part, open-label study to evaluate the effect of food or a proton-pump inhibitor and to evaluate the relative bioavailability of different tablet formulations in healthy post-menopausal female participants. CCI

[redacted] ARV-471 C_{max} for [redacted] and AUC_{inf} for [redacted], as compared with fasted conditions. A single oral dose of 200 mg ARV-471 has been well tolerated in healthy participants, and [redacted] of [redacted] were reported. Based on the safety data of ARV-471 and prior clinical experience described above, the 200 mg single dose is expected to be well tolerated by healthy adult participants.

Rosuvastatin is a synthetic statin that has been developed for the treatment of patients with dyslipidemia. Rosuvastatin is administered orally and approximately 50% of the drug is absorbed resulting in 20% absolute bioavailability[8]. As the maximum contribution of intestinal BCRP to restricting rosuvastatin absorption is 50%, the impact of inhibiting intestinal BCRP by ARV-471 on rosuvastatin systemic exposure is expected to be less than 2-fold. Inhibition of liver BCRP by ARV-471 is not expected to play a major role in potential rosuvastatin systemic exposure increase.

In a single dose escalation study, rosuvastatin was safe and well tolerated at doses up to 80 mg[9]. The most common AEs reported were headache and rash. There was no evidence of a relationship between the frequency of AEs and rosuvastatin dose. No SAEs were reported. The therapeutic dose of rosuvastatin is from 5 mg up to 40 mg, and most DDI studies involving rosuvastatin as a substrate were conducted at the 10 mg or 20 mg dose level[10,11,12,2]. Administration with food (low-fat or high-fat) was reported to result in a near 40% reduction of rosuvastatin exposure[13] while CRESTOR® USPI claims administration with food did not affect the AUC of rosuvastatin. However, 10 mg single dose with potential food effect should still lead to sufficient amount in the plasma for detection.

Rosuvastatin is not extensively metabolized through CYP450 pathway and [redacted] Thus, the single dose combination of 200 mg ARV-471 and 10 mg rosuvastatin is expected to be generally safe and well tolerated by healthy participants.

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and/or female participants of non-childbearing potential must be 18 to 65 years of age, inclusive at the time of signing ICD. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

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

Other Inclusion Criteria:

3. BMI of 17.5 to 32 kg/m2; and a total body weight ≥45 kg (110 lb).

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

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

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

    - Positive test result for SARS-CoV-2 infection at the time of admission.

2. Pregnant female participants; breastfeeding female participants; Male participants with partners currently pregnant; fertile male participants who have partners of

childbearing potential and are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 90 days after the last dose of investigational product.

3. Participants with known history of hypersensitivity to statin medication. Participants with known history of sensitivity to ARV-471 or rosuvastatin or any of the formulation components of ARV-471 or rosuvastatin.

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

Prior/Concomitant Therapy:

5. Use of prescription or nonprescription medications, including vitamins, dietary and herbal supplements, within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Additionally, a longer washout is required for the medications below:

    - Moderate or strong CYP3A/BCRP inducers which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.

    - Moderate or strong CYP3A/BCRP inhibitors which are prohibited within 14 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.

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

7. A positive urine drug test.

8. Screening supine BP ≥140 mm Hg (systolic) when age <60 years, ≥150 mm Hg (systolic) when age ≥60 years, or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) when age <60 years, ≥150 mm Hg (systolic) when age ≥60 years or, ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

9. 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.

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

    - AST **or** ALT level >ULN;
    - Total bilirubin level >ULN;
    - Renal impairment as defined by an eGFR in adults of ≤60 mL/min/1.73m^2. Based upon participant age at screening, eGFR is calculated using the recommended CKD-EPI formulas in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events.
    - Hypothyroidism

Other Exclusion Criteria:

11. History of use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day.

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

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

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

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

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

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the standard breakfast on Period 1 Day 1 and Period 2 Day 1. Participants must also abstain from all food and drink (except water) at least 4 hours post rosuvastatin dose.

- Water may be consumed without restriction except from 1 hour before to 1 hour after rosuvastatin dosing. In Period 2 Day 1, water is not allowed after ARV-471 dosing and before rosuvastatin dosing.

- On dosing days (Day 1 of Period 1 and 2), participants will be provided the recommended standard breakfast of approximately 700 calories with a fat content of approximately 35% 2 hours (120 minutes) prior to rosuvastatin administration. This meal will be consumed within a 20-minute period without study intervention (Period 1 Day 1) or with ARV-471 (Period 2 Day 1) administered within approximately 10 minutes after completion of the meal. The provided meal must be completely consumed prior to administration of ARV-471 (a single oral 200 mg dose with approximately 240 mL of ambient temperature water).

- On non-dosing days, participants can resume normal intake of both food and water.

- Noncaffeinated drinks (except grapefruit or grapefruit related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after rosuvastatin dosing.
- Dinner will be provided approximately 9 to 10 hours after rosuvastatin dosing.
- An evening snack may be permitted.
- Participants will refrain from consuming grapefruit, grapefruit containing products or grapefruit related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 14 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. 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 refrain from consuming red wine from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.4. 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 study medication dosing.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to ARV-471 (PF-07850327) 100 mg tablet and rosuvastatin (CRESTOR®) 10 mg tablet.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	ARV-471 (PF-07850327)	Rosuvastatin (CRESTOR®)
Arm Name (group of participants receiving a specific treatment or no treatment)	Period 2 only	Period 1 and 2
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	100 mg	10 mg
Dosage Level(s)	200 mg	10 mg
Route of Administration	Oral	Oral
Use	Experimental	Experimental treatment to assess as probe substrate in current DDI study
IMP or NIMP/AxMP	IMP	NIMP/AxMP
Sourcing	Provided centrally by the sponsor	Provided locally by the trial site
Packaging and Labeling	Study intervention will be provided in high-density polyethylene bottle with child resistant cap. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in high-density polyethylene bottle with child resistant cap. Each bottle will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	ARV-471 (PF-07850327)	Rosuvastatin (CRESTOR®)

ARV-471 tablets will be supplied to the CRU as packaged bottles and labeled according to local regulatory requirements. The bottles will be provided to the site for dispensing by the pharmacy.

Rosuvastatin (CRESTOR®) tablets will be supplied locally by the CRU.

6.1.1. Administration

Period 1 Day 1: Following an overnight fast of at least 10 hours, participants will start the recommended standard breakfast approximately 2 hours (120 minutes) prior to rosuvastatin (as 1 tablet of 10 mg) dosing. The standard breakfast will be required to be completely consumed within an approximately 20-minute period.

Participants will receive study medication at approximately 0900 hours (plus or minus 2 hours). Investigator site personnel will administer rosuvastatin (as 1 tablet of 10 mg) with ambient temperature water to a total volume of approximately 240 mL approximately 2 hours (120 minutes) after the start of the standard breakfast. Participants will swallow the study medication whole and will not manipulate or chew the medication prior to swallowing.

Period 2 Day 1: Following an overnight fast of at least 10 hours, participants will start the recommended standard breakfast prior to administration of ARV-471 (as 2 tablets of 100 mg) and rosuvastatin (as 1 tablet of 10 mg). The standard breakfast will be required to be completely consumed within an approximately 20-minute period.

Participants will receive study medication at approximately 0900 hours (plus or minus 2 hours). Investigator site personnel will administer ARV-471 (as 2 tablets of 100 mg) approximately 10 minutes after the completion of the meal with ambient temperature water to a total volume of approximately 240 mL. Investigator site personnel will administer rosuvastatin (as 1 tablet of 10 mg) approximately 1.5 hours (90 minutes) after the ARV-471 dosing with ambient temperature water to a total volume of approximately 240 mL, which is approximately 2 hours (120 minutes) after the start of the standard breakfast. Participants will swallow the study medication whole and will not manipulate or chew the medication prior to swallowing.

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.

ARV-471 and rosuvastatin tablets will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). A second staff member will verify the dispensing. The

tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

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

The investigator will assign participant numbers to the participants as they are screened for the study.

6.4. Blinding

This is an open label study.

6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention.

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

6.6. Dose Modification

No dose modification is anticipated.

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

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

6.8. Treatment of Overdose

For this study, any dose of ARV-471 greater than 200 mg or rosuvastatin greater than 10 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose of ARV-471 or rosuvastatin.

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

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

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

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

5. Obtain a blood sample for PK analysis within 1 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription medications, including vitamins, dietary and herbal supplements, are prohibited in this study. A washout of 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention is required. Additionally, a longer washout is required for the medications below:

- Moderate or strong CYP3A/BCRP inducers which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.

- Moderate or strong CYP3A/BCRP inhibitors which are prohibited within 14 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.

Females taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study treatment.

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

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

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

- AE requiring discontinuation at the discretion of investigator;
- Positive COVID-19 test.

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

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

7.1.1. Liver Injury

Reasons for permanent discontinuation of study intervention due to potential liver injury are described in Appendix 6.

7.1.2. ECG Changes

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

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

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

7.1.3. Potential Cases of Acute Kidney Injury

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

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

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

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

7.1.4. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided.

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:

- Unacceptable toxicity;
- Significant protocol violation;
- Lost to follow-up;
- Refused further study procedures;
- Study terminated by sponsor;
- Withdraw consent;
- Death;
- Investigator decision.

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 return to the clinic for/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 and Screening 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.

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 170 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

Physical examinations are to be performed at the nominal timepoints specified in the SoA. Additional physical examinations will be permitted, as necessary, to ensure appropriate collection of safety data.

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.

8.3.3. 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 the baseline measurement on Period 1 Day 1. 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 undergo COVID-19 related measures per CRU procedures.

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 intervention (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, 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 intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek 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 female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 28 days after the last dose of ARV-471.

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

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

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

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

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

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

the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not Applicable.

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

Not Applicable.

8.4.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that

these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOP.

AEs that are considered AESIs for ARV-471 include [redacted] Based on current understanding of the safety profile, no expedited reporting by the investigator to sponsor is required for non-serious AESIs. Additional details and mitigation strategies are summarized in Section 2.3.1.

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

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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

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

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

8.5. Pharmacokinetics

Blood sample collection for measurements of plasma concentration of rosuvastatin is detailed in Section 8.5.1. Blood sample collection for measurements of plasma concentration of ARV-471 and ARV-473 is detailed in Section 8.5.2.

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

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

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.

8.5.1. Pharmacokinetics for rosuvastatin

Blood samples of approximately 4 mL, to provide approximately 1.6 mL plasma, will be collected for measurement of plasma concentrations of rosuvastatin 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.

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

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

CCI

[redacted]

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 the laboratory manual and supporting documentation.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

No statistical hypotheses will be tested in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Full analysis set	All participants who take at least 1 dose of study intervention.
Safety analysis set	All participants enrolled and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration Set	All participants who are in the Safety Analysis Set and have at least 1 rosuvastatin concentration measured.
PK Parameter Set	All participants who are in the Safety Analysis Set and have at least 1 PK parameter of interest (C_{max} or AUC of rosuvastatin).

9.3. Statistical Analyses

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

9.3.1. Pharmacokinetic Analysis

The plasma PK parameters will be derived from the concentration-time profiles as detailed in Table 5 for each analyte and treatment if applicable. Actual PK sampling times will be used in 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 5. PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the concentration-time profile from time 0 to the time of last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
AUC_{inf}[a]	Area under the concentration-time profile from time 0 extrapolated to infinite time.	$AUC_{last} + (C_{last}*/k_{el})$, Where $C_{last}*$ is the predicted concentration at the last quantifiable time point estimated from the log-linear regression analysis and k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
C_{max}	Maximum concentration	Observed directly from data.
C_{last}	Last measurable observed concentration	Observed directly from data.
T_{max}	Time for C_{max}	Observed directly from data.
T_{last}	Time for C_{last}	Last measurable observed concentration
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$,. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F[a]	Apparent clearance	$Dose/(AUC_{inf})$
V_z/F [a]	Apparent volume of distribution	$Dose/(AUC_{inf}*k_{el})$
CCI [redacted]	[redacted]	[redacted]

a. if data permit and as appropriate.

9.3.2. Statistical Methods for PK Data

The plasma concentrations of rosuvastatin 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 period for each analyte 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. For comparison of rosuvastatin AUC_{inf} and C_{max} with and without ARV-471, box and whisker plots of these parameters will be plotted by period.

Natural log transformed parameters (AUC_{inf} [if data permit)], AUC_{last}, and C_{max}) of rosuvastatin will be analyzed using a mixed effect model with treatment as fixed effects and participant 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. Rosuvastatin administered alone will be the reference treatment and ARV-471 co-administered with rosuvastatin will be the test treatment.

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

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

9.3.3.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

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

9.3.4. Other Analyses

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

No 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 sufficient number of participants will be screened to ensure that at least 12 participants will be enrolled in the study.

The sample size is empirically selected and is not based on hypothesis testing. A sample size of 12 PK evaluable participants who have at least 1 of the rosuvastatin PK parameters of primary interest (AUC_{inf} or C_{max}) is expected to provide 90% CIs for the difference between treatments of CCI and CCI on the natural log scale for AUC_{inf} and C_{max}, respectively, with 80% coverage probability. The following table presents the width of 90% CI for different estimated effects:

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf}	100%	0.8569, 1.1671	0.3102
	120%	1.0282, 1.4005	0.3722
	140%	1.1996, 1.6339	0.4343
	160%	1.3710, 1.8673	0.4963
	180%	1.5423, 2.1007	0.5584
	200%	1.7137, 2.3341	0.6204

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
C_{max}	100%	0.8387, 1.1923	0.3536
	120%	1.0065, 1.4308	0.4243
	140%	1.1742, 1.6692	0.4950
	160%	1.3420, 1.9077	0.5657
	180%	1.5097, 2.1461	0.6364
	200%	1.6774, 2.3846	0.7071

These calculations are based on estimates of within subject standard deviations of CCI and CCI for $\log_e$ AUC_{inf} and $\log_e$ C_{max} respectively, as average intrasubject standard deviations obtained from previously completed rosuvastatin crossover studies CCI [redacted] and one external study[13].

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.

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 maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

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

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

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor's designee (Pfizer CRU).

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

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

10.1.9. 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

CCI [redacted]

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.

10.1.12. Transfer of Obligations Statement

CCI [redacted]

For the purposes of this protocol, "sponsor" refers to Pfizer.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) MCV, MCH, MCHC	BUN/Urea and creatinine CystatinC and eGFR Glucose (fasting) Calcium Creatine kinase Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	<u>Local dipstick:</u> pH[a] Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin <u>Laboratory:</u> Microscopy and culture[b]	COVID-19 testing (per CRU procedures) Urine drug screening[c] <u>At screening:</u> • FSH[d] • TSH • HIV • HbsAg • HbcAb • HBsAb[e] • HCVAb

a. May be performed on dipstick or pH-meter device
b. Urinary culture only if deemed appropriate by the investigator (only if UTI is suspected and/or and urine dipstick is positive for nitrites or leukocyte esterase or both).
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. For confirmation of postmenopausal status only.
e. Hepatitis B surface antibody will be performed as reflex testing for any participant who is HBsAg and HBcAb positive.

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. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. 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 90 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s).

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual or homosexual 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.

  - Agree to use a male condom, a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; and (b) agrees not to donate eggs (ova, oocytes) for the purpose of reproduction at least 28 days after the last dose of study intervention; and (c) is not a WOCBP (see definition in Section 10.4.3).

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable 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 study intervention 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[14]

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

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 May 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 May Qualify as SAEs

- QTcF prolongation >500 ms.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS complex>120 ms).
- New-onset right bundle branch block (QRS complex>120 ms).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

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

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

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
ADR	adriamycin
AE	adverse event
AESI	adverse event of special interest
AI	aromatase inhibitor
AKI	acute kidney injury
ALT	alanine aminotransferase
ARV-471	PF-07850327
ARV-473	the epimer metabolite of ARV-471
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-144}	area under the concentration-time curve from time zero to 144 hours
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{tau}	area under concentration-time curve over dosing interval
AUC_{last}	area under the concentration-time profile from time 0 to the time of last quantifiable concentration (C_{last}).
AV	atrioventricular
AxMP	auxiliary medicinal product
BA	bioavailability
BBS	Biospecimen Banking System
BC	breast cancer
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BE	bioequivalence
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
CES	carboxylesterase
CFR	Code of Federal Regulations
CI	confidence interval

Abbreviation	Term
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL/F	apparent clearance after oral dose
C_{last}	last quantifiable concentration
C_{max}	maximum observed concentration
CNS	central nervous system
CoA	coenzyme A
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 Trial Information System
CTMS	Clinical Trial Management System
CV	cardiovascular
CYP	cytochrome P450
CYP3A	Cytochrome P450 3A
CYP3A4	Cytochrome P450 3A4
DC_{50}	Concentration at 50% degradation
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DL	drug load
DLT	dose-limiting toxicity
E-DMC	External Data Monitoring Committee
EC	ethics committee; exclusion criteria
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
ECT	ecarin clotting time
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
Egfr	estimated glomerular filtration rate
ER	estrogen receptor
Era	estrogen receptor a
Erb	estrogen receptor b
eSAE	electronic serious adverse event
ESR1	estrogen receptor 1
ET	endocrine therapy

Abbreviation	Term
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	The United States Food and Drug Administration
FE	food effect
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gammaglutamyl transferase
GI	gastrointestinal
GI_{50}	concentration for 50% of maximal inhibition of cell proliferation
GLP	Good Laboratory Practice
Hb	hemoglobin
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HCT	hematocrit
HCVAb	hepatitis C antibody
HER2	human epidermal growth factor receptor 2
Herg	human ether-à-go-go-related gene
Hgb	hemoglobin
HIV	human immunodeficiency virus
HMG	hydroxy-3-methylglutaryl
HR	heart rate
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
HV	healthy volunteer
IB	Investigator's Brochure
IC	inclusion criteria
IC_{50}	half-maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IMNM	Immune-mediated necrotizing myopathy
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IoR	Importer of Record
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)

Abbreviation	Term
K	Proportionality constant for Bedside and Modified Schwartz Equations (kidney function)
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	terminal phase rate constant calculated by a linear regression of the log-linear concentration time curve
K_m	Michaelis–Menten constant that corresponds to the substrate concentration at which the uptake rate is half of the maximum transport rate
LBBB	left bundle branch block
LD_{50}	the dose required to kill half the members of a tested population after a specified test duration
LFT	liver function test
log_e	the exponent or power to which a base must be raised to yield a given number
MATE1	multidrug and toxin extrusion protein 1
MATE2	multidrug and toxin extrusion protein 2, also known as MATE2-K
mBC	metastatic breast cancer
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MQI	medically qualified individual
CCI [redacted]	[redacted]
NIMP	non-investigational medicinal product
NOAEL	no-observed-adverse-effect level
NOD/scid	nonobese diabetic/severe combined immunodeficiency
NOEL	no observed effect level
N/A	not applicable
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OCT2	organic cation transporter 2
P-gp	P-glycoprotein
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)
PPI	proton pump inhibitor

Abbreviation	Term
PR	pulse rate
PROTAC®	PROteolysis TArgeting Chimeric
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTH	parathormone
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
qual	qualitative
rBA	relative bioavailability
RBC	red blood cell
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
Scr	serum creatinine
Scys	serum cystatin C
SD	single dose
SDD	spray-dried dispersion
SERD	selective estrogen receptor degrader or downregulator
SERM	selective estrogen receptor modulator
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal elimination half-life
T bili	total bilirubin
TEAE	treatment emergent adverse event
TGI	tumor growth inhibition
THC	tetrahydrocannabinol
TK	toxicokinetics
T_{last}	the time for last quantifiable concentration
T_{max}	the time for maximum observed concentration
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States Prescribing Information

Abbreviation	Term
UTI	urinary tract infection
VE	venous embolism
V_z/F	apparent volume of distribution after oral dose
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WT	wild type

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