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 DABIGATRAN IN HEALTHY PARTICIPANTS

Study Intervention Number:	PF-07850327
Study Intervention Name:	ARV-471
US IND Number:	CCI
EudraCT/CTIS Number:	2022-003397-23
ClinicalTrials.gov ID:	Not Applicable
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C4891008
Phase:	1

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

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

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Rationale:

ARV-471 is considered an in vitro P-gp inhibitor. Although ARV-471 does not show inhibition against P-gp in a CCI assay format up to the maximum soluble concentration of CCI and ARV-471 inhibits P-gp with an IC_{50} of CCI in an 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.

The theoretical maximum concentration of ARV-471 in the GI tract after a single oral dose of 200 mg ARV-471 is 0.8 mg/mL (1.1 mM) assuming a gastric fluid volume of 250 mL that is approximately CCI-fold higher than CCI. While the in vitro risk assessment for CCI can be CCI for drugs that have poor solubility (BCS Class II or IV), the in vivo potential for ARV-471 to inhibit P-gp activity in human GI tract cannot be excluded. Therefore, a clinical interaction study with a P-gp substrate is needed to assess the effect of ARV-471 on P-gp activity.

Based on available data to date, it is possible that administration of a P-gp substrate, dabigatran etexilate (as mesylate), with ARV-471 may lead to increased plasma exposures of dabigatran. The purpose of this study is to estimate the effect of ARV-471 on the PK of dabigatran 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 the single dose PK of dabigatran in healthy participants	• Plasma total dabigatran (sum of unconjugated and glucuronide-conjugated dabigatran) PK parameters alone and following administration of a single 200 mg dose of ARV-471: C_{max}, AUC_{inf} (AUC_{last} if AUC_{inf} cannot be estimated)
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of dabigatran etexilate (as mesylate) alone and following administration with a single 200 mg dose of ARV-471	• Safety: 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 200 mg dose of ARV-471	• CCI [redacted], as data permit and as appropriate
	• Other total dabigatran PK parameters: 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 a P-gp substrate, dabigatran etexilate (as mesylate), in healthy male participants and healthy female participants with nonchildbearing potential. An attempt will be made to enroll more than 50% participants as female participants with nonchildbearing potential in this study since ARV-471 is being developed for the treatment in a population that is predominately female.

Number of Participants:

A sufficient number of participants will be screened to ensure that at least 24 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 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.

Study Population:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

Age and Sex:

1. Healthy male and/or female participants of non-childbearing potential who are overtly healthy as determined by medical evaluation and are between the ages of 18 and 70 years, inclusive at the time of signing the ICD. Healthy participant is defined as no clinically relevant co-morbidities or abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG, or clinical laboratory tests.

2. Female participants of non-childbearing potential must meet at least one of the following criteria:

    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum FSH level confirming the post-menopausal state;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy;

    c. Have medically confirmed ovarian failure.

    All other female participants (including females with tubal ligations and females that do NOT have a documented hysterectomy, bilateral oophorectomy and/or ovarian failure) will be considered to be of childbearing potential and therefore not eligible.

Other Inclusion Criteria:

3. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

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

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).

    - Evidence or 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.

2. Pregnant female participants, breastfeeding female participants, female participants of childbearing potential. Male participants with partners currently pregnant; male participants of childbearing potential who 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. Active bleeding or risk of bleeding including prior personal or familiar history of abnormal bleeding, hereditary or acquired coagulation or platelet disorder or abnormal coagulation test (PT/INR or PTT/aPTT greater than upper limit of normal) result at screening. Any significant risk factor for major bleeding and this may include but not limited to current or recent GI ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

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, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products within 7 days or 5 half-lives (whichever is

longer) prior to the first dose of study intervention or a longer washout is required for those that fall into the categories below:

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

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

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 or alcohol breath test at the discretion of investigator.

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

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, STT 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 >1.0 × ULN;

    - Total bilirubin level > 1.0 × ULN;

    - Renal impairment as defined by an eGFR in adults of < 75 mL/min/1.73 m^2. Based upon participant age at screening, eGFR is calculated using the

recommended formulas in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events;

- PT/INR or PTT/aPTT > 1.0 × ULN.

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

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

16. 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.

17. History of sensitivity to ARV-471 or dabigatran etexilate (as mesylate) or any of the formulation components of ARV-471 or dabigatran etexilate (as mesylate).

Study Arms and Duration:

This fixed sequence study will consist of 2 periods: Period 1 = single oral dose of dabigatran etexilate (as mesylate) alone; Period 2 = single oral dose of dabigatran etexilate (as mesylate) + single oral dose of ARV-471 with staggered dosing. A washout of at least 4 days must occur between the 2 successive single doses of dabigatran etexilate (as mesylate). Following

administration of dabigatran etexilate (as mesylate) and/or ARV-471 in each period, participants will undergo serial PK sampling.

Study Intervention(s)		
Intervention Name	ARV-471 (PF-07850327)	Dabigatran etexilate (as mesylate) (PRADAXA®)
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	75 mg
Route of Administration	Oral	Oral
Use	Experimental	Experimental treatment to assess as endpoints
IMP or NIMP/AxMP	IMP	NIMP/AxMP

Statistical Methods:

Dabigatran PK exhibits relatively high inter-individual variability. Sample size calculation was based on average intra-participant standard deviations obtained from [redacted] internal dabigatran crossover studies CCI [redacted] and [redacted] previously completed external dabigatran study. Based on these studies, the estimates of within-participant standard deviations of CCI and CCI for $\log_e$ AUC_{inf} and $\log_e C_{max}$, respectively, were used in the calculation. A sample size of 24 participants will provide 90% CIs for the difference between treatments of CCI and of CCI on the natural logarithmic scale for AUC_{inf} and C_{max} respectively with 80% coverage probability.

Total dabigatran PK parameters following a single dose administration will be derived from total dabigatran plasma concentration versus time profiles using non-compartmental methods, as data permit and as appropriate. Total dabigatran PK parameters will be summarized descriptively by treatment. Individual participant total dabigatran PK parameters for AUC_{inf} (as data permit), AUC_{last}, and C_{max} will be plotted by treatment and overlaid with geometric means. Total dabigatran concentrations will be listed and summarized descriptively by PK sampling time and treatment. Summary profiles (means and medians) of concentration versus time data will be plotted by treatment on linear and semi-log scale. Individual participant concentration vs time profiles will also be presented.

CCI [redacted]

Natural log transformed parameters (AUC_{inf} [as data permit], AUC_{last}, and C_{max}) of total dabigatran will be analyzed using a mixed effect model with treatment as a fixed effect 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. Dabigatran etexilate (as mesylate) administered alone will be the reference treatment and ARV-471 administered with dabigatran etexilate (as mesylate) will be the test treatment.

Ethical Considerations:

ARV-471 alone or in combination with dabigatran etexilate (as mesylate) will not provide any clinical benefit to healthy participants in this study. Any anticipated benefit to participants would be in terms of contribution to the process of developing a new therapy for the treatment of ER+/HER2- BC.

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 (Dabigatran etexilate [as mesylate] alone) and Period 2 (Dabigatran etexilate [as mesylate] with ARV-471)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screen**	**Period 1**					**Period 2**			**Follow-Up**	**Early Termination/ Discontinua-tion**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 1**	**Day 2**	**Day 3**	**28-35 Days**		• All screening should be done ≤28 days before the first dose. • 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	X	X	X	X	X	X			• Participants will be admitted to the CRU on the day prior to Period 1 dosing (Day -1). • Participants will be discharged on Day 3 of Period 2 following PK sampling and study activities.
Inclusion/ exclusion criteria	X	X										• See Sections 5.1 and 5.2 for details
Medical/ medication history	X	X										• Medical history will include but not limited to a history of prior drug, alcohol, and tobacco use, as well as blood donation within prior 60 days. Medical history will be recorded at Screening and updated on Day -1 of Period 1 only.
PE	X	X										• A full PE, 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 (Dabigatran etexilate [as mesylate] alone) and Period 2 (Dabigatran etexilate [as mesylate] with ARV-471)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screen**	**Period 1**					**Period 2**			**Follow-Up**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 1**	**Day 2**	**Day 3**	**28-35 Days**		• All screening should be done ≤28 days before the first dose. • 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, coagulation tests 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. • Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.
PTT/aPTT	X	X				X			X		X	• Participants will also be monitored clinically for signs of bleeding.
PT/INR	X	X										
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 the participant 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.
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 Trip-licate			X	X		X		X	• Singlet 12-lead ECG will be taken at specified times. Triplicate ECG will be collected at pre-dose on Day 1 of Period 1 only. 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. Refer to Table 2 and Table 3 for singlet 12-lead ECG collections.
Vital signs (BP/PR)	X		X			X	X		X		X	• Refer to Table 2 and Table 3 for 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			• Performed per local procedures

Table 1. Period 1 (Dabigatran etexilate [as mesylate] alone) and Period 2 (Dabigatran etexilate [as mesylate] with ARV-471)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screen**	**Period 1**					**Period 2**			**Follow-Up**	**Early Termination/ Discontinuation**	**Notes**
Days Relative to Day 1	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 1**	**Day 2**	**Day 3**	**28-35 Days**		• All screening should be done ≤28 days before the first dose. • 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.
Dabigatran etexilate (as mesylate) administration			X				X					• Refer to Section 6.1.1 for details of administration requirement.
ARV-471 administration							X					• Refer to Section 6.1.1 for details of administration requirement.
PK blood sampling			X	X	X		X	X	X		X	• Please refer to Table 2 and Table 3 for 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.
Retained Research Sample for biomarkers (Prep B2)			X									• 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 8.1.
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(s) at discharge, or in the case of an early discontinuation. These activities may include physical examination, safety laboratory, contraception check, single 12-lead ECG and supine blood pressure and pulse rate.
Serious and non-serious AE monitoring	X	X	X	X	X	X	X	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 dabigatran etexilate [as mesylate]): PK and ECG Sampling Schedule

Visit Identifier Abbreviations used in this table maybe found in Appendix 10	**Period 1 (single oral dose of dabigatran etexilate [as mesylate])**													**Notes**
Study Day	**Day 1**									**Day 2**		**Day 3**	**Day 4**	
Hours Before/After dabigatran etexilate (as mesylate) Dose	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	• Hour 0 = pre-dose sample collection.
Dabigatran etexilate (as mesylate) administration	X													• Refer to Section 6.1.1 for additional details of administration requirement.
Dabigatran (total) PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X		• Blood samples (4 mL) for PK analysis will be taken at specified timepoints. • Refer to Section 8.5 for additional details.
12-Lead ECG	X (triplicate)												X	• Singlet ECG will be taken at specified timepoints. Triplicate ECG will be collected at pre-dose on Day 1 of Period 1 only. All ECG assessments will be made after at least a 5-minute rest in supine position and prior to any blood draws or vital sign measurement.
Vital signs (BP/PR)	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.

Table 3. Period 2 (Single oral dose of dabigatran etexilate [as mesylate] with ARV-471): PK and ECG Sampling Schedule

Visit Identifier Abbreviations used in this table maybe found in Appendix 10	**Period 2 (single oral dose of dabigatran etexilate [as mesylate] with single oral dose of ARV-471)**													**Notes**
Study Day	**Day 1**										**Day 2**		**Day 3**	
Hours Before/After dabigatran etexilate (as mesylate) Dose	**-1.5**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	• Hour 0 = pre-dose sample collection for dabigatran; CCI [redacted]
ARV-471 administration	X													• Refer to Section 6.1.1 for details of administration requirement.
Dabigatran etexilate (as mesylate) administration		X												• Refer to Section 6.1.1 for details of administration requirements.
CCI [redacted]	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran (total) PK blood sampling		X	X	X	X	X	X	X	X	X	X	X	X	• Pre-dose PK samples will also be collected prior to dabigatran etexilate (as mesylate) dosing. Blood samples (4 mL) for PK analysis will be taken at specified timepoints. Refer to Section 8.5 for details.
12-Lead ECG	X						X						X	• Singlet ECG will be taken at specified 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.
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 any blood draws if scheduled at the same time.

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- BC.

2.1. Study Rationale

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 an 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. ARV-471 is considered an in vitro inhibitor of P-gp (ARV-471 [PF-07850327] Investigator's Brochure)

The theoretical maximum concentration of ARV-471 in the GI tract after a single oral dose of 200 mg ARV-471 is 0.8 mg/mL (1.1 mM) assuming a gastric fluid volume of 250 mL that is approximately CCI CCI than CCI While the in vitro risk assessment for CCI can be CCI for drugs that have poor solubility (BCS Class II or IV), the in vivo potential for ARV-471 to inhibit P-gp activity in human GI tract cannot be excluded. Therefore, a clinical interaction study with a P-gp substrate is needed to assess the effect of ARV-471 on P-gp activity.

Based on available data, it is possible that administration of a P-gp substrate, dabigatran etexilate (as mesylate), with ARV-471 may lead to increased plasma exposures of dabigatran (active drug). The purpose of this study is to estimate the effect of ARV-471 on the PK of dabigatran 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 CCI decreases 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 CCI . 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 ([redacted] and ER ([redacted] mutations in a [redacted] manner similar to fulvestrant. In the same study, ARV-471 inhibited growth of these [redacted] cell lines with GI_{50} values of [redacted] and [redacted] for ER [redacted] and ER [redacted] 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 preclinical species (mouse, rat, dog, and monkey) was characterized by a [redacted] clearance ([redacted] to [redacted] of hepatic blood flow), [redacted] tissue distribution ([redacted] to [redacted]), [redacted] to [redacted] $t_{1/2}$ ([redacted] to [redacted] hours), and [redacted] to [redacted] oral bioavailability ([redacted] ARV-471 can interconvert to its epimer, ARV-473. Plasma exposure of ARV-473 relative to ARV-471 upon ARV-471 dosing was limited in animal PK and TK studies.

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.[1] This study indicated CYP3A4 as the [redacted] isoform responsible for CYP metabolism of ARV-471 (accounting for [redacted]

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 2 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 2 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.

Dose-dependent increase in ARV-471 exposure was observed when ARV-471 was administered as an oral solution in the mouse (10, 30, and 100 mg/kg), rat (30, 100, and 300 mg/kg), dog (15, 45, 90, 200 and 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] Investigator's Brochure 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 investigator's brochure and Appendix 9.

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 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 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

CCI 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 toxicokinetic profile of ARV-471 and its epimer ARV-473 when administered QD orally (by gavage). The toxicity program includes up to 3-month GLP-compliant repeat-dose studies in rats and dogs, GLP-compliant in vitro bacterial reverse mutation (Ames) assay, 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 The CCI in the CCI were CCI and considered to be due to the CCI of ARV-471. The CCI of CCI (compared to controls) of CCI were noted in CCI in the CCI. No CCI have been noted in the CCI Subsequently, the CCI there were CCI in the CCI CCI. Based on the CCI data evaluating CCI and function of ARV-471 in rat and dog, it is concluded that the CCI finding observed only in the CCI was a CCI and CCI to CCI The NOAEL for CCI was determined to be the CCI 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. ARV-471 CCI in CCI, CCI with CCI of the drug. The CCI was identified as the NOAEL for CCI. A NOAEL was CCI for CCI 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 and were also observed in the CCI. In males and females at CCI the C_{max} was CCI and CCI and AUC_{0-24} was CCI and CCI on Day 91, respectively.

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 and 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, ARV-471 has been well-tolerated across total daily doses of 30 mg to 700 mg in patients with mBC. No DLTs were observed and most TRAEs were Grade 1 or 2. 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.

The ongoing Phase 1 clinical pharmacology study, Study CCI, is evaluating the effect of food or a PPI and the rBA 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 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 data support continued clinical development of ARV-471 in ER+/HER2- advanced breast cancer.

Refer to ARV-471 [PF-07850327] Investigator's Brochure 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 [redacted] across the cohorts. The geometric mean $t_{1/2}$ following a single oral 200 mg dose was approximately [redacted] under fed condition. Food intake increased ARV-471 C_{max} and AUC_{inf} 3- to 2-fold, respectively, as compared with fasted conditions. Data indicated [redacted] on exposure of ARV-471 when administered with a [redacted] (approximately [redacted] with a fat content of approximately [redacted] Exposures of ARV-471 (C_{max} and AUC) of [redacted] drug-loaded SDD tablets (tests) were similar to the [redacted] drug-loaded SDD tablets (reference) when administered with a [redacted].

Refer to ARV-471 [PF-07850327] Investigator's Brochure for additional information.

2.3. Benefit/Risk Assessment

ARV-471 alone or in combination with dabigatran etexilate (as mesylate) is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and pharmacokinetic 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 dabigatran etexilate (as mesylate) (PRADAXA®) agent is the European approved SmPC.

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 characterized.	Participants will receive a single 200 mg dose 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 ARV-471-mBC-101. CCI 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 and at additional time points post study intervention dosing during the study intervention period. 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 immobility due to recent biopsy procedure, and a Grade 3 serious CCI case assessed as unlikely related to ARV-471 by the investigator, were reported in the FIH Study CCI.	Participants will receive a single 200 mg dose ARV-471 in Period 2 in this study. No VE AE was reported after a single dose of ARV-471 at any dose level in study ARV-471-mBC-101. Participants with a history of clinically significant CCI events are excluded from participation in the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Dabigatran etexilate (as mesylate)		
Increased risk of bleeding	Dabigatran etexilate (as mesylate) should be used with caution in conditions with an increased risk of bleeding or with concomitant use of medicinal products affecting hemostasis by inhibition of platelet aggregation. Bleeding can occur at any site during therapy. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site.	A single oral dose of 75 mg dabigatran etexilate (as mesylate) will be administered in both periods in this study with a minimum washout of 4 days between doses. Although dabigatran does not generally require routine anticoagulant monitoring, the measurement of dabigatran-related anticoagulation is applied in this study to detect excessive high exposure to dabigatran in the presence of additional risk factors. Measurement of PTT/aPTT in the study (screening and additional specified time points post dose in both period) as well as PT/INR measurement at Screening and Day -1 in Period 1. In addition, CBC to monitor platelets, Hgb, HCT, etc. as well as hemodynamic monitoring such as BP and PR are also being evaluated in the study. In additional, participants will be monitored clinically for signs of bleeding. Participants considered in imminent need for surgery or with elective surgery scheduled to occur during the study will be excluded from this study.

a. CCI -1373, Table 11, ARV-471 CCI estimate (90% CI): CCI
b. Study CCI CSR Table 14.2.2.3.

2.3.2. Benefit Assessment

ARV-471 alone or in combination with dabigatran etexilate (as mesylate) will not provide any clinical benefit to healthy participants in this study. Any anticipated benefit to participants would be in terms of contribution to the process of developing a new therapy for the treatment of ER+/HER2- BC.

2.3.3. Overall Benefit/Risk Conclusion

ARV-471 alone or in combination with dabigatran etexilate (as mesylate) are not expected to provide any clinical benefit to healthy participants in this study. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with ARV-471 and/or dabigatran etexilate (as mesylate) 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 the single dose pharmacokinetic of dabigatran in healthy participants.	• Plasma total dabigatran (sum of unconjugated and glucuronide-conjugated dabigatran) PK parameters alone and following administration of a single 200 mg dose of ARV-471: C_{max}, AUC_{inf} (AUC_{last} if AUC_{inf} cannot be estimated).
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of dabigatran etexilate (as mesylate) alone and following administration with a single 200 mg dose of ARV-471	• Safety: 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 200 mg dose of ARV-471	• CCI [redacted]
	• Other total dabigatran PK parameters: 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 to estimate the effect of a single oral ARV-471 dose on the PK of a P-gp substrate, dabigatran etexilate (as mesylate), in healthy male participants or healthy female participants of nonchildbearing potential. An attempt will be made to enroll more than 50% participants as female participants with

nonchildbearing potential in this study since ARV-471 is being developed for the treatment in a population that is predominately female.

This study will consist of 2 periods with a fixed sequence treatment design. On Period 1 Day 1, a standard breakfast will be provided prior to dosing. The standard breakfast will be completely consumed within an approximately 20-minute period. A single dose of 75 mg dabigatran etexilate (as mesylate) (as 1 capsule of 75 mg) will be administered approximately 2 hours (120 minutes) after starting the standard breakfast. To adequately remove any drug effects of dabigatran, a minimum washout period of 4 days is followed after dabigatran etexilate (as mesylate) administration on Period 1 Day 1. Serial PK samples will be collected up to 48 hours after single dose administration to determine dabigatran PK parameters (total).

On Period 2 Day 1, a standard breakfast will be provided prior to ARV-471 and dabigatran etexilate (as mesylate) dosing. The standard breakfast will be completely consumed within an approximately 20-minute period. A single dose of 200 mg ARV-471 (as 2 tablets of 100 mg) will be administered approximately 10 minutes after the completion of the breakfast. A single dose of 75 mg dabigatran etexilate (as mesylate) (as 1 capsule of 75 mg) will be administered approximately 1.5 hour (90 minutes) after the start of ARV-471 dosing, which is approximately 2 hours (120 minutes) after the start of the breakfast. Serial PK samples will be collected up to 48 hours post dabigatran etexilate (as mesylate) dosing to determine the single dose PK parameters of CCI CCI dabigatran (total).

A sufficient number of participants will be screened to ensure that at least 24 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). Medical history and results of physical examination, physical measurements, vital signs, 12-lead ECGs, and clinical laboratory evaluations will determine eligibility.

Participants will report to the CRU at least 12 hours prior to Day 1 dosing in Period 1 and will be required to stay in the CRU for 8 days and 7 nights. Washout period will begin after the first dose of study treatment.

Fixed-Sequence	Period 1		Period 2	
Screening	**Day 1-4**	**At least 4-Day washout**	**Day 1- 3**	**Follow-up**
All screening should be done 2 to 28 days before the first dose	(Reference) 75 mg single oral dose of dabigatran etexilate (as mesylate) administered approximately 2 hours (120 minutes) after the start of a standard breakfast (Period 1 Day 1)	The washout will begin after the first dose of study medication	(Test) 200 mg single oral dose of ARV-471 administered approximately 30 minutes after the start of the standard breakfast and 75 mg single oral dose of dabigatran etexilate (as mesylate) administered approximately 1.5 hours (90 minutes) after the start of ARV-471 dosing, which is approximately 2 hours (120 minutes) after the start of the breakfast (Period 2 Day 1).	Follow-up must occur 28 to 35 days after administration of the final dose of study intervention

Period 1 Day 1 (dabigatran etexilate [as mesylate]):

- 75 mg dabigatran etexilate (as mesylate) as commercially available PRADAXA® (as 1 capsule of 75 mg).

Period 2 Day 1 (ARV-471 + dabigatran etexilate [as mesylate]):

- 200 mg single dose of ARV-471 (PF-07850327) (as 2 tablets of 100 mg) and
- 75 mg dabigatran etexilate (as mesylate) as commercially available PRADAXA® (as 1 capsule of 75 mg).

ARV-471 (PF-07850327) will be supplied by Pfizer as 100 mg tablets. Dabigatran etexilate (as mesylate) (PRADAXA®) as 75 mg capsule 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 7 days/6 nights (excluding screening and follow-up contact). Participants will be discharged on Period 2 Day 3 following completion of all assessments.

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

4.2. Scientific Rationale for Study Design

4.2.1. Probe P-gp Substrate Selection

Dabigatran etexilate (as mesylate) will be used as the P-gp probe substrate in this study. Dabigatran etexilate (as mesylate) is a small molecule prodrug with low systemic exposure that is rapidly absorbed and converted to dabigatran (active form) upon administration via CES hydrolysis in the intestine and liver. Dabigatran is a direct thrombin inhibitor with antithrombotic effects. Dabigatran etexilate (as mesylate) is a selective probe substrate of intestinal P-gp but not dabigatran.[3] Thus, modulation of intestinal P-gp activity will affect dabigatran etexilate (as mesylate) absorption, which is reflected in dabigatran plasma exposure. The PK of dabigatran is highly sensitive to changes in P-gp activities given the low bioavailability. Dabigatran etexilate (as mesylate) has been recommended as a probe for intestinal P-gp inhibition by regulatory agencies.[2]

It is important to note that inter-individual variability for dabigatran PK tend to be high possibly due to variabilities in individual P-gp and CES activities.[3] In a DDI study, dosing time of dabigatran relative to perpetrator dosing time was one of the factors that affected interaction between dabigatran and verapamil (P-gp inhibitor). The maximum effect (~2.5-fold increase in exposure) was observed when dabigatran etexilate (as mesylate) was given 1 hour after a single dose of verapamil.[17] Thus, a staggered dosing approach will be used in this study.

CCI

[redacted]

Other P-gp probe substrates include digoxin and fexofenadine. Fexofenadine is also one of the preferred substrates of intestinal P-gp. However, characterization of DDI effect can be challenging due to overlapping drug transporters that also regulate fexofenadine disposition (eg, OATP1A2,[5] OATP1B3,[5] OATP2B1,[5] OAT3,[6] BSEP,[7] MRP2,[8] MRP3[7]). Single dose rifampicin (OATP inhibitor and P-gp inhibitor) has been shown to increase fexofenadine exposures up to 4-fold.[9] Additionally, those homozygous for the SLCO1B1 521T>C SNP (associated with reduced OATP1B1 activity), were shown to have 127% higher fexofenadine exposures as compared to participants with the reference SLCO1B1 genotype (521TT).[10] Furthermore, probenecid, an index inhibitor of OATs, was shown to increase fexofenadine AUC by ~50% while decreasing its CL_r by ~73%.[11]

In the past, digoxin has been commonly used as the probe P-gp substrate. Digoxin is a cardiac glycoside indicated for treatment of cardiac arrhythmias and heart failure. The

clinical use of digoxin has decreased over the last 20 years due to approval of medications with a wider therapeutic range. Digoxin is not selective for P-gp in vitro or in vivo and exhibits low PK sensitivity to P-gp inhibition. Digoxin is not selective to intestinal P-gp and also substrate of hepatobiliary/renal P-gp. It can be a probe substrate of choice in scenarios, such as co-administration with digoxin would be expected in a clinical setting to ensure safety and/or predominate impact on hepatobiliary or renal P-gp (eg, pro-drug, intravenous drug, major circulating metabolites shown to be P-gp inhibitor).

Based on the above considerations for each probe substrate, dabigatran etexilate (as mesylate) has been selected for this study based on its preferable safety and pharmacokinetic profiles compared to digoxin and fexofenadine.

4.2.2. Administration of Study Interventions 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 indicated that CCI ARV-471 C_{max} and AUC_{inf} CCI to CCI, respectively, as compared with fasted conditions. Cross cohort comparison showed similar or higher exposure increase using a CCI (approximately CCI with a fat content of approximately 35%) versus a high fat meal (approximately CCI, consisting of at least CCI calories from protein, CCI calories from carbohydrates and CCI calories from fat) with the prior formulation (20% drug load with CCI SDD). ARV-471 is recommended to be CCI for clinical studies. New formulation (CCI drug load with CCI SDD) showed similar exposure compared with prior formulation (CCI drug load with CCI SDD). The median T_{max} is CCI hours and the $t_{1/2}$ of ARV-471 after a single 200 mg dose is approximately CCI hours.

Considering the available data known to date and formulation used in this study (CCI drug load with CCI SDD), ARV-471 will be CCI (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 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 in the toxicology studies in both rat and dog are known to express both ERa and ERb. Findings in the 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 in animals administered . A finding of was ARV-471-related in recovery sacrifice males included of the and which correlated with , and . These findings in may have reflected the after degradation of the ER, compared to the A contributing factor to the effects on the 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 with CCI . CCI 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	CCI (NOEL)	CCI	CCI	CCI
Rat	28 days	CCI (NOEL)	CCI	CCI	CCI
Rat	91 days	CCI (NOEL)	CCI	CCI	CCI
Dog	7 days	CCI (NOAEL)	CCI	CCI	CCI
Dog	28 days	CCI (NOAEL)	CCI	CCI	CCI
Dog	91 days	CCI (NOAEL)	CCI	CCI	CCI

Table 4. Exposure Margin Determination for [redacted] 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]

a. AUC_{tau} taken from IB Version 4.0 for 200 mg dose of ARV-471 of [redacted] ng•h/mL in participants with mBC.
b. AUC_{inf} taken from preliminary data of [redacted] rBA – test formulation arm ([redacted] drug load and [redacted] SDD) for a single 200 mg dose of ARV-471 of [redacted] ng•h/mL in healthy participants.

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

While a single dose of ARV-471 may carry [redacted] of producing [redacted] based on the [redacted] of ARV-471, the risk of [redacted]. Learnings from published literature support the position that male tissues would fully recover and there would not be a permanent effect on male fertility.[12] The chronic administration of fulvestrant (selective estrogen receptor degrader) in dogs followed by a recovery period of 6 months demonstrated no long-term impact on fertility in male dogs (FDA website summary basis of approval) and full recovery of male tissues. These key data support the reversibility and resumed normal function in adult male animals when estrogen signaling is reengaged. Additionally, literature review of a total of 21 drugs 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.[13,14] 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.[13,14] 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."[13] Meistrich et al also pointed out that these 2 drugs, thiotepa and adriamycin, are strong mutagens, [redacted].[14]

In summary, given that the [redacted] tested provided a [redacted] of [redacted] in the 3-month toxicity study, the [redacted] to [redacted] in dogs shown in all studies to date, the [redacted] 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 [redacted] is assessed to be [redacted] 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. Dabigatran 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.[15]

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 (see Appendix 4).

4.2.5.1. Females – Non-Childbearing Potential

Female participants of childbearing potential will not be allowed in this study.

Female participants of non-childbearing potential must meet at least one of the criteria defined in Section 5.1 (all other female participants, including females with tubal ligations, will be considered to be of childbearing potential; Inclusion Criterion #1 and #2).

4.2.5.2. Males

All fertile male participants who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and continue for at least 90 days after the last dose of investigational product (ARV-471). The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his partner from the permitted list of contraception methods and instruct the participant in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or his or her designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or the participant's partner.

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 dose will be used in this study. This is the current, proposed Phase 3 dose of ARV-471. A single oral dose of 75 mg dabigatran etexilate (as mesylate) 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 CCI ARV-471 C_{max} and AUC_{inf} CCI, respectively, as compared with CCI CCI A single oral dose of 200 mg ARV-471 has been well tolerated in healthy participants, and CCI of CCI 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.

Dabigatran is approved to prevent or treat thromboembolic conditions, including the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The clinical dose of dabigatran etexilate (as mesylate) varies depends on indication, organ function, and region (SmPC vs USPI). 150 mg BID is the commonly approved clinical dose across different countries and 220 mg QD or higher doses are also approved in the EU.

Dabigatran was well tolerated after administration of single oral doses of 10 – 400 mg in healthy participants. Seven of 40 participants reported an AE, all of mild to moderate severity. The most frequently reported AE was headache. In the multiple ascending dose cohort, dabigatran was well tolerated with 14 participants reported at least 1 AE and all were mild to moderate in severity.[16] In a DDI study, verapamil (a strong P-gp inhibitor) increased AUC_{inf} and C_{max} of dabigatran (dosed as 150 mg single dose) by 143% and 179%, respectively. Fifteen of the 20 participants reported treatment-related AEs and the most common related AEs were nervous system and gastrointestinal disorders. All AEs were of mild to moderate intensity, and there were no serious AEs, and all resolved by the end of the study.[17]

Regulatory guidance does not provide recommendation on the dose of dabigatran etexilate (as mesylate) when it is used as P-gp probe substrate in DDI studies. Some DDI studies available in the published literature utilized a 150 mg single oral dose when using dabigatran etexilate (as mesylate) probe substrate;[17,18] A single oral 75 mg dose of dabigatran etexilate (as mesylate) dose has also been used.[19,20] A larger magnitude of effect (if any) would be expected following a lower dose of dabigatran etexilate (as mesylate). Thus, a single 75 mg oral dose of dabigatran etexilate (as mesylate) will be used for this study.

Results of clinical trials have indicated that inhibition of P-gp activity generally results in changes in dabigatran exposures that are ≤2.5-fold and the increase was not associated with pharmacodynamic interactions.[21] Given the above discussion and considering that ARV-471 is also a BCS class IV drug (low solubility and permeability), ARV-471 CCI to CCI dabigatran by CCI than CCI. In addition, dabigatran 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. Thus, the single dose combination of 200 mg ARV-471 and 75 mg dabigatran etexilate (as mesylate) should be well-tolerated by healthy adult 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

Participant eligibility should be reviewed and documented by an appropriate member of the investigator's study team before participants are included in the study.

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

Age and Sex:

1. Healthy male and/or female participants of non-childbearing potential who are overtly healthy as determined by medical evaluation and are between the ages of 18 and 70 years, inclusive at the time of signing the ICD. Healthy participant is defined as no clinically relevant co-morbidities or abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG, or clinical laboratory tests.

2. Female participants of non-childbearing potential must meet at least one of the following criteria:

    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum FSH level confirming the post-menopausal state;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy;

c. Have medically confirmed ovarian failure.

All other female participants (including females with tubal ligations and females that do NOT have a documented hysterectomy, bilateral oophorectomy and/or ovarian failure) will be considered to be of childbearing potential and therefore not eligible.

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

Other Inclusion Criteria:

3. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

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

   - Evidence or 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.

2. Pregnant female participants, breastfeeding female participants, female participants of childbearing potential. Male participants with partners currently pregnant; male participants of childbearing potential who 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. Active bleeding or risk of bleeding including prior personal or familiar history of abnormal bleeding, hereditary or acquired coagulation or platelet disorder or abnormal coagulation test (PT/INR or PTT/aPTT greater than upper limit of normal)

result at screening. Any significant risk factor for major bleeding and this may include but not limited to current or recent GI ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

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, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention or a longer washout is required for those that fall into the categories below:

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

    - Moderate or strong CYP3A/P-gp 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 or alcohol breath test at the discretion of investigator.

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

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, STT 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 >1.0 × ULN;
    - Total bilirubin level >1.0 × ULN;
    - Renal impairment as defined by an eGFR in adults of < 75 mL/min/1.73 m^2. Based upon participant age at screening, eGFR is calculated using the recommended formulas in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events;
    - PT/INR or PTT/aPTT >1.0 × ULN.

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

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

16. 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.

17. History of sensitivity to ARV-471 or dabigatran etexilate (as mesylate) or any of the formulation components of ARV-471 or dabigatran etexilate (as mesylate).

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 (approximately CCI [redacted] with a fat content of approximately CCI 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 dabigatran etexilate (as mesylate) dose on Period 1 Day 1 and Period 2 Day 1, unless otherwise indicated (see water restriction below). Additionally, food or drinks (including water) will not be allowed after ARV-471 dosing and before dabigatran etexilate (as mesylate) dosing in Period 2 Day 1.

- Water may be consumed without restriction except from 1 hour before to 1 hour after study intervention dosing. Water intake consumed only during the standard breakfast on Period 2 Day 1 is allowed.

- On Period 1 Day 1 following an overnight fast of at least 10 hours, participants will be provided the standard breakfast (approximately CCI [redacted] with a fat content of approximately CCI approximately 2 hours (120 minutes) prior to dabigatran etexilate (as mesylate) dosing. This breakfast will be completely consumed within an

approximately 20-minute period. Dabigatran etexilate (as mesylate) will be administered with approximately 240 mL of ambient temperature water at approximately 2 hours (120 minutes) after starting breakfast.

- On Period 2 Day 1 following an overnight fast of at least 10 hours, participants will be provided the standard breakfast (breakfast must be the same as provided in Period 1 Day 1). This breakfast will be completely consumed within an approximately 20-minute period. ARV-471 will be administered approximately 10 minutes after the completion of the meal with approximately 240 mL of ambient temperature water. Dabigatran etexilate (as mesylate) will be administered approximately 1.5 hour (90 minutes) after the start of ARV-471 dosing, with approximately 240 mL of ambient temperature water, which should be approximately 2 hours (120 minutes) after the start of the breakfast.

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

- Lunch will be provided at least 4 hours after dabigatran etexilate (as mesylate) dosing.

- Dinner will be provided approximately 9 to 10 hours after dabigatran etexilate (as mesylate) dosing.

- An evening snack may be permitted.

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

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

5.3.3. Caffeine, Alcohol, and Tobacco

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

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

- Participants will 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 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 dabigatran etexilate (as mesylate) (PRADAXA®) 75 mg capsule.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	ARV-471 (PF-07850327)	Dabigatran etexilate (as mesylate) (PRADAXA®)
Arm Name (group of participants receiving a specific treatment or no treatment)	Period 2 only	Periods 1 and 2
Type	Drug	Drug
Dose Formulation	Tablet	Capsule
Unit Dose Strength(s)	100 mg	75 mg
Dosage Level(s)	200 mg	75 mg
Route of Administration	Oral	Oral
Use	Experimental	Experimental treatment to assess as endpoint

Study Intervention(s)		
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)	Dabigatran etexilate (as mesylate) (PRADAXA®)

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

Dabigatran etexilate (as mesylate) (PRADAXA®) capsules 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 dabigatran etexilate (as mesylate) (as 1 capsule of 75 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 dabigatran etexilate (as mesylate) (as 1 capsule of 75 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. No additional food will be allowed for at least 4-hours post dose.

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 dabigatran etexilate (as mesylate) (as 1 capsule of 75 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 moderate breakfast with ambient temperature water to a total volume of approximately 240 mL. Investigator personnel will administer dabigatran etexilate (as mesylate) (as 1 capsule of 75 mg) approximately 1.5 hours (90 minutes) after the start of ARV-471 dosing with ambient temperature water to a total volume of approximately 240 mL, which should be approximately 2 hours (120 minutes) after the start of the standard breakfast. Participants will swallow the study medications

whole and will not manipulate or chew the medications prior to swallowing. No additional food will be allowed for at least 4-hour post dabigatran dose.

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.

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

6.3. Assignment to Study Intervention

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

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

6.4. Blinding

This is an open-label study.

6.4.1. 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. 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 dabigatran etexilate (as mesylate) greater than 75 mg within a 24-hour time period will be considered an overdose.

An accidental overdose of dabigatran may lead to increased risk of bleeding. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment, and investigate the source of bleeding. For dabigatran, a specific reversal agent (idarucizumab) is available.[22]

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

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 day 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, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products **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 or a longer washout is required for those that fall into the categories below:

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

- Moderate or strong CYP3A/P-gp inhibitors which are prohibited within 14 days or 5 halflives (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.

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with ARV-471. For dabigatran, the specific reversal agent (idarucizumab) is available. Standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- AE requiring discontinuation 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.

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 in a given period are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.4. 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.

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

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

The total blood sampling volume for individual participants in this study is approximately 209 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.

8.1.1. Baseline Procedures

The following procedures will be completed:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Confirm proper contraception is being used.
- Demographics (race, age, gender and ethnicity).
- Obtain medical history, including but not limited to history of prior drug, alcohol and tobacco use as well as blood donation within 60 days prior.
- Obtain complete medication history of all prescription or nonprescription drugs, including vitamins, and dietary and herbal supplements, grapefruit/grapefruit

containing products, and Seville orange/Seville orange containing products taken within 28 days prior to the planned first dose.

- Conduct full physical examination including height and weight to obtain BMI for eligibility criteria. The Screening physical examination may be performed on Day -1, Period 1.
- Collect single 12-lead ECG.
- Obtain supine blood BP and PR following at least a 5-minute rest in a supine position.
- Following at least a 4-hour fast, collect blood and urine specimens for the following:
  - Safety laboratory tests (eg, urinalysis, hematology, chemistry, coagulation tests);
  - Urine drug test (alcohol breath and blood test at discretion of investigator);
  - Serum FSH concentration for any female who has been amenorrheic for at least 12 consecutive months without an alternative pathological or physiological reason;
  - Collect blood for HBsAb, HBsAg, HBcAb, HCVAb, and HIV testing.

To prepare for study participation, participants will be instructed on the use of the Lifestyle Considerations and Concomitant Treatment(s) 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 full physical examination without genitourinary evaluation will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A limited 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 baseline measurements. 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 Related Measures

Participants will undergo COVID-19 related measures per local 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 CCI [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 Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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

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

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

8.5. Pharmacokinetics

Blood sample collection for measurements of plasma concentration of dabigatran (total) is detailed in Section 8.5.1. CCI [redacted] Plasma samples may be used for evaluation of dabigatran etexilate CCI [redacted]

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

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 total dabigatran

Blood samples of approximately 4 mL, to provide approximately 1.5 to 1.8 mL plasma, will be collected for measurement of plasma concentrations of total dabigatran (sum of unconjugated and conjugated dabigatran) 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 total dabigatran. Each plasma sample will be divided into 2 aliquots (1 each for shipment to bioanalytical lab and back up sample at study site). Samples collected for analyses of total dabigatran 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 CCI .

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

CCI

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.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.7.1. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

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

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

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

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

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

No statistical hypothesis will be tested in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assigned 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 enrolled and assigned to study intervention and who take at least 1 dose of study intervention.
Safety analysis set	All participants in the full analysis set. 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 measurable concentration of CCI [redacted].
PK Parameter Set	All participants who are in the Safety Analysis Set and have at least 1 PK parameter of interest for CCI [redacted].

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 for total dabigatran will be derived (as data permit and as appropriate) from the concentration time profiles as detailed in Table 5 for CCI and treatment. 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.

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Table 5. Plasma PK Parameters

Parameter	Definition	Method of Dete rmination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of last quantifiable concentration (C_{last}).	Linear/Log trape zoidal method.
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time.	AUC_{last} + (C_{last}* k_{el}), Where C_{last}* s he predicted plasma concenti ation at the last qu an tifiable time point estimated from the log- re gression analysis. linear
C_{max}	Maximum plasma concentration	Observe directly from data.
C_{last}	Last measurable observed concentration	Observe directly from data.
T_{max}	Time for C_{max}	Observe directly from data.
T_{last}	Time for C_{last}	Observe directly from data.
$t_{1/2}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, whe e k_{el} is the ul phase rate CCI ermin log- linear concentra l those data points judged to ion-time curve. na l log-linear decline will be u On or .
CL/F[a]	Apparent clearance	Dose/(AUC_{inf})
V_z/F[a]	Apparent volume of distribution	Dose/(AUC_{inf} *k el)
CCI		

Table 5. Plasma PK Parameters

Parameter	Definition	Method of Determination
CCI		

a. if data permits and as appropriate.

9.3.2. Statistical Methods for PK Data

Natural log transformed parameters (AUC_{inf} [if data permit], AUC_{last}, and C_{max}) of total dabigatran (sum of unconjugated or glucuronide-conjugated dabigatran) will be analyzed using a mixed effect model with treatment as a fixed effect 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. Dabigatran administered alone will be the reference treatment and ARV-471 co-administered with dabigatran will be the test treatment.

Total dabigatran PK parameters following a single dose administration will be derived from the plasma concertation versus time profiles using non-compartmental methods, as data permit and as appropriate. The plasma concentrations of total dabigatran will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles of the plasma concentration time data will be plotted by treatment for CCI 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 total dabigatran only, AUC_{inf} (as data permit), AUC_{last}, and C_{max} with and without ARV-471, box and whisker plots of these parameters will be plotted by treatment for CCI.

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CCI [redacted].

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 treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

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

Safety QTcF Assessment

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

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. Changes from baseline will be defined as the change between the postdose QTcF value and the 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 sample size of 24 participants will provide 90% confidence intervals for the difference between treatments of CCI and of CCI on the natural logarithmic scale for AUC_{inf}

and C_{max} respectively with 80% coverage probability. The following table presents the width of 90% confidence interval for a range of effects possibly seen in the study:

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf}	80%	0.6165, 1.0381	0.4216
	100%	0.7706, 1.2977	0.5270
	120%	0.9247, 1.5572	0.6324
	140%	1.0789, 1.8167	0.7378
	160%	1.2330, 2.0762	0.8433
	180%	1.3871, 2.3358	0.9487
	200%	1.5412 ,2.5953	1.0541
	220%	1.6954, 2.8548	1.1595
	240%	1.8495, 3.1144	1.2649
	260%	2.0036, 3.3739	1.3703
C_{max}	80%	0.5758, 1.1114	0.5356
	100%	0.7198, 1.3893	0.6694
	120%	0.8638, 1.6671	0.8033
	140%	1.0077, 1.9450	0.9372
	160%	1.1517, 2.2228	1.0711
	180%	1.2957, 2.5007	1.2050
	200%	1.4396, 2.7785	1.3389
	220%	1.5836, 3.0564	1.4728
	240%	1.7275, 3.3342	1.6067
	260%	1.8715, 3.6121	1.7405

These calculations are based on estimates of within-participant standard deviations of CCI and CCI for $\log_e$ AUC_{inf} and $\log_e$ C_{max}, respectively, as average intra-participant standard deviations obtained from previously completed dabigatran crossover studies (clinical studies CCI [redacted]) and CCI external study.[17]

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

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 Pfizer CRU.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the 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) If Hb/RBC abnormal: MCV, MCH, MCHC	BUN/Urea and creatinine CystatinC and eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Local dipstick: pH[a] Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Laboratory: Microscopy and culture[b]	SARS-CoV-2 RT-PCR aPTT/PTT PT/INR Urine drug screening[c] Alcohol breath test (at the disretion of the investigator) At screening: • FSH[d] • 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 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 may be routinely tested or only if HBsAg and/or HBcAb are positive. HBsAb due to vaccination is permissible.

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

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

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

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

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

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

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

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

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

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

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.

- The investigator may change 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 intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; 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) at least 1 of the following conditions applies:

- 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."

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

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

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

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

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

Inker LA et al. N Engl J Med. 2021;385:1737-49.[23]

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: Overview of GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Table 7. Overview of GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Study Number (Sponsor Reference[a])	Study Title	Test Facility in Which the Study Was Conducted	Date Range for Study Conduct[b]	CRO Contact
Safety Pharmacology				
DJ06CT (ARV471-00059-00-INVITRO)	ARV-471: Effects on hERG Tail Current Recorded from Stably Transfected HEK-293 Cells	Covance Laboratories Limited Woolley Road Alconbury Huntingdon Cambridgeshire PE28 4HS UK	02 Apr 2020 to 15 Apr 2021	PPD
Repeat-Dose Toxicity				
8382301 (ARV-471-TOX-003)	ARV-471: 28-Day GLP Oral Gavage Toxicity and Toxicokinetic Study in Rats with a 28-Day Recovery Phase	Covance Laboratories Inc. 671 South Meridian Road Greenfield, Indiana 46140 USA	13 Aug 2018 to 06 Sep 2019	PPD
8382302 (ARV-471-TOX-004)	ARV-471: 28-Day GLP Oral Gavage Study in Dogs with a 28-Day Recovery	Covance Laboratories Inc. 671 South Meridian Road Greenfield, Indiana 46140 USA	28 Aug 2018 to 12 Sep 2019	PPD
21GR195	3-Month Oral Gavage Toxicity Study of ARV-471 in Beagle Dogs	Pfizer Worldwide Research & Development Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA	26 Oct 2021 to 06 Jul 2022	NA
Genotoxicity				
8427274 (ARV471-00061-00-INVITRO)	ARV-471: Bacterial Reverse Mutation Assay	Covance Laboratories Ltd. Otley Road, Harrogate North Yorkshire, HG3 1PY England	22 May 2020 to 19 Nov 2020	PPD
8427276 (ARV471-00062-00-INVITRO)	ARV-471: In Vitro Human Lymphocyte Micronucleus Assay	Covance Laboratories Ltd. Otley Road, Harrogate North Yorkshire, HG3 1PY England	28 May 2020 to 23 Nov 2020	PPD

Table 7. Overview of GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Study Number (Sponsor Reference[a])	Study Title	Test Facility in Which the Study Was Conducted	Date Range for Study Conduct[b]	CRO Contact
Carcinogenicity				
NA				
Reproductive and Developmental Toxicity				
NA				
Local Tolerance				
NA				
Other Toxicity Studies				
20325699 (ARV471-00073-00-INVITRO)	Neutral Red Uptake Phototoxicity Assay of ARV-471 in BALB/c 3T3 Mouse Fibroblasts	Charles River Laboratories, Inc. 905 Sheehy Drive Horsham, PA 19044 USA	17 Dec 2021 to 17 Mar 2022	PPD

hERG = human ether-à-go-go-related gene; GLP = Good Laboratory Practice; HEK= human embryonic kidney; NA = not applicable.
a. Where applicable, the sponsor reference number is provided in parentheses.
b. Date study protocol signed to date study report signed.

Table 8. Facilities for GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Facility	Inspection Date	Documents provided
Pfizer Worldwide Research & Development Drug Safety Research & Development Eastern Point Road Groton, CT 06340 USA	04 Jan 2021 to 08 Jan 2021	FDA EIR
Covance Laboratories Limited Woolley Road Alconbury Huntingdon Cambridgeshire PE28 4HS UK	03 Apr 2020; 12 Jul 2020 to 13 Jul 2020 02 Dec 2020 to 03 Dec 2020; 05 Feb 2021 to 15 Feb 2021; 14 Apr 2021 to 15 April 2021	Quality Assurance Inspection Reports Audit Reports
Covance Laboratories Inc. 671 South Meridian Road Greenfield, Indiana 46140 USA	March 2020	FDA EIR
Covance Laboratories Ltd. Otley Road, Harrogate North Yorkshire, HG3 1PY England	NA	GLP Declaration Statement

Table 8. Facilities for GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Facility	Inspection Date	Documents provided
Charles River Laboratories, Inc. 905 Sheehy Drive Horsham, PA 19044 USA	12 Jul 2021 to 16 Jul 2021	FDA EIR

10.10. Appendix 10: 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
aPTT	activated partial thromboplastin time
ARV-471	PF-07850327
ARV-473	the epimer metabolite of ARV-471 (PF-07850327)
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-144}	area under the concentration-time curve from time zero to 114 hours
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AUC_{inf}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{tau}	area under plasma concentration-time curve at steady state over dosing interval
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of last measurable concentration
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
BSEP	bile salt export pump
BUN	blood urea nitrogen
CBC	complete blood count
CES	carboxylesterase
CFR	Code of Federal Regulations

Abbreviation	Term
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL/F	apparent clearance of drug from eg, plasma
C_{last}	last quantifiable concentration
CLr	clearance value
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
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
CV	cardiovascular
CYP	cytochrome P450
DAB	dabigatran
DABE	dabigatran etexilate (as mesylate)
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dosing limiting toxicity
dTT	diluted thrombin time
E-DMC	External Data Monitoring Committee
EC	ethics committee
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
ESR	erythrocyte sedimentation rate
ESR1	Estrogen Receptor 1
ET	endocrine therapy
EU	European Union

Abbreviation	Term
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FE	food effect
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl 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
HEK	human embryonic kidney
HER2	human epidermal growth factor receptor 2
hERG	human ether-à-go-go-related gene
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
HV	healthy volunteer
IB	Investigator's Brochure
IC_{50}	50% inhibitive concentration
ICD	Informed Consent Document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IoR	Importer of Record
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)
K	Proportionality constant for Bedside and Modified Schwartz Equations (kidney function)
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	first-order elimination rate constant

Abbreviation	Term
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}	lethal dose 50%
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]
MRP	multidrug resistance-associated protein
NA	not applicable
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
NOEL	no observed effect level
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
PR	pulse rate
PROTAC®	PROteolysis TArgeting Chimeric
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTH	parathormone

Abbreviation	Term
PTT	partial thromboplastin time
PVC	premature ventricular contraction
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
RT-PCR	reverse transcription polymerase chain reaction
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
STT	ST-segment and T-wave
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal phase half-life
T bili	total bilirubin
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
THC	tetrahydrocannabinol
T_{last}	time for C_{last}
TK	toxicokinetics
T_{max}	time to reach C_{max}
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
UTI	urinary tract infection
VE	venous embolism

Abbreviation	Term
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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