Title Page

AN INTERVENTIONAL, PHASE 1, OPEN-LABEL, FIXED SEQUENCE, 2-PERIOD STUDY TO ESTIMATE THE EFFECT OF MULTIPLE DOSES OF ITRACONAZOLE ON THE PHARMACOKINETICS OF SINGLE DOSE ARV-471 IN THE FED CONDITION IN HEALTHY ADULT MALES, AND FEMALES OF NONCHILDBEARING POTENTIAL

Study Intervention Number:	PF-07850327
Study Intervention Name:	ARV-471
US IND Number:	N/A
EudraCT Number:	2022-003282-38
ClinicalTrials.gov ID:	N/A
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4891009
Phase:	1
Brief Title: Phase 1, Open-label, Fixed Sequence, 2-Period Study to Estimate the Effect of Multiple Doses of Itraconazole on the Pharmacokinetics of Single Dose ARV-471	

Document History

Document	Version Date
Amendment 2	12 January 2023
Amendment 1	21 October 2022
Original protocol	20 July 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 2 (12 January 2023)

Overall Rationale for the Amendment: Responses to regulatory queries warranted protocol amendments.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1.3. Schedule of Activities Table 3. PK, ECG, BP, and PR Sampling Schema for Period 1 and Table 4. PK, ECG, BP, and PR Sampling Schema for Period 2	12-Lead ECG measurement at 4 hours post-dose was changed to 6 hours post-dose	The 6-hour timepoint more closely aligns with the observed ARV-471 Tmax range in patients and healthy volunteers.	Nonsubstantial
4.3. Justification for Dose	Table 9 and Table 10 were reformatted and safety exposure margins were updated. In-text exposure margins were updated to correspond with changes in the tables.	Tables were made more comprehensive by replacing point estimates with a range of predicted safety exposure margins.	Nonsubstantial
4.2. Scientific Rationale for Study Design - Males	Safety exposure margins were updated in Table 5. In-text exposure margins were updated to correspond with changes in the table.	Table 5 was made more comprehensive by replacing point estimates with a range of predicted safety exposure margins.	Nonsubstantial
10.9. Appendix 9: Overview of GLP Safety Pharmacology and Toxicology Testing Program	Table formatting was updated and additional studies were included. CRO contact information was removed and date of	Updates were made to comply with Clinical Trials Facilitation and Coordination Group guidelines.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
for ARV-471 (PF-07850327)	completion of the final report was added.		
1.1. Synopsis Regulatory Agency Identification Number(s)	US IND number was removed.	This study will be conducted in Belgium and not submitted under the US IND.	Nonsubstantial
Title Page US IND Number	US IND number was removed.	This study will be conducted in Belgium and not submitted under the US IND.	Nonsubstantial
10.10 Appendix 10: Abbreviations	Added abbreviations to the list.	Added abbreviations relative to this amendment.	Nonsubstantial

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Interventional, Phase 1, Open-Label, Fixed Sequence, 2-Period Study to Estimate the Effect of Multiple Doses of Itraconazole on the Pharmacokinetics Of Single Dose ARV-471 in the Fed Condition in Healthy Adult Males, and Females of Nonchildbearing Potential

Brief Title: Phase 1, Open-label, Fixed Sequence, 2-Period Study to Estimate the Effect of Multiple Doses of Itraconazole on the Pharmacokinetics of Single Dose ARV-471

Regulatory Agency Identification Number(s):

US IND Number:	N/A
EudraCT Number:	2022-003282-38
ClinicalTrials.gov ID:	N/A
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4891009
Phase:	1

Rationale:

Itraconazole and its primary metabolite (hydroxy-itraconazole) are specific strong inhibitors of CYP3A. Since ARV-471 is a substrate for CYP3A, concomitant administration of multiple doses of itraconazole along with ARV-471 may lead to increased systemic exposure of ARV-471. The objective of this study is to estimate the effect of multiple doses of itraconazole on the PK of ARV-471.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	
• To estimate the effect of multiple doses of itraconazole on the pharmacokinetics of a single oral 200 mg dose of ARV-471.	**Primary:** • Plasma AUC_{inf} and C_{max} of ARV-471 and ARV-473, as data permits (AUC_{last} if AUC_{inf} cannot be estimated).
Secondary:	
• To estimate the effect of multiple doses of itraconazole on the pharmacokinetics of a single oral 200 mg dose of ARV-471.	• Plasma AUC_{last}, T_{max}, $t_{1/2}$, CL/F and V_z/F of ARV-471 and ARV-473, as data permits.
• To evaluate the safety and tolerability of a single oral 200 mg dose of ARV-471 administered to healthy participants in the absence and presence of multiple doses of itraconazole under fed conditions.	• Safety laboratory tests, physical examination, vital signs, electrocardiograms, concomitant medication and adverse event monitoring.

Overall Design:

This is a Phase 1, open-label, 2-period, fixed-sequence crossover study to estimate the effect of multiple doses of the strong CYP3A inhibitor, itraconazole, on the pharmacokinetics of

ARV-471 and its epimer, ARV-473, in healthy male and female participants of nonchildbearing potential.

Number of Participants:

Approximately 12 participants will be enrolled in the study.

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

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Healthy male and/or female participants of non-childbearing potential who are overtly healthy as determined by medical evaluation including medical history, physical exam, laboratory tests, vital signs and standard 12-lead ECGs and are between the ages of 18 and 65 years, inclusive at the time of signing the ICD.

2. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg.

3. Evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.

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

Exclusion Criteria

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

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

2. Pregnant female participants, breastfeeding female participants, female participants of childbearing potential.

3. Male participants with partners currently pregnant; fertile male participants who are unwilling or unable to use a highly effective method of contraception.

4. Use of prescription or non-prescription medications, including vitamins, herbal and dietary supplements, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products within 7 days prior to the first dose of study intervention with the exception of:

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

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

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

6. A positive urine drug test or alcohol breath test at discretion of investigator.

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

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

9. AST **or** ALT level >1.0 × ULN.

10. Total bilirubin level >1.0 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

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

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

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

14. Known hypersensitivity or previous adverse events associated with azole antifungals or any of the formulation components of ARV-471.

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

16. Renal impairment as defined by an eGFR<60 mL/min/1.73m^2.

Study Arms and Duration:

The study will consist of 2 periods; Period 1 = single dose of ARV-471 alone and Period 2 = multiple doses of itraconazole + single dose of ARV-471. A washout period of at least 10 days must occur between the 2 successive single doses of ARV-471 in this study. Following administration of ARV-471 in each period, participants will undergo serial PK sampling.

Study Intervention(s)		
Intervention Name	ARV-471 (PF-07850327)	Itraconazole
Type	Drug	Drug
Dose Formulation	Tablet	Oral Solution
Unit Dose Strength(s)	100 mg	10 mg/mL
Dosage Level(s)	200 mg	200 mg
Route of Administration	Oral	Oral
Use	Experimental	Experimental treatment to assess an endpoint
IMP or NIMP/AxMP	IMP	NIMP/AxMP
Sourcing	Provided centrally by the sponsor	Sourced 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 (20 mL itraconazole 10 mg/mL oral solution) will be dispensed from commercial Sporanox® into oral syringes.
Current/Former Names or Aliases	ARV-471 (PF-07850327)	Itraconazole (Sporanox®)

Statistical Methods:

A sample size of 12 PK evaluable participants who have at least 1 of the ARV-471/ARV-473 PK parameters of primary interest (AUC_{inf} or C_{max}) is expected to provide 90% CIs for the difference between treatments of CCI and CCI on the natural log scale for AUC_{inf} and C_{max}, respectively, with 80% coverage probability.

ARV-471 and ARV-473 PK parameters following a single dose administration of ARV-471 will be derived from the ARV-471 and ARV-473 plasma concentration versus time profiles using non-compartmental methods as data permit. ARV-471 and ARV-473 PK parameters (primary endpoints: AUC_{inf} and C_{max}; secondary endpoints: AUC_{last}, T_{max}, $t_{1/2}$, CL/F, and V_z/F) will be summarized descriptively by treatment. Individual participant parameters for AUC_{inf}, AUC_{last} and C_{max} will be plotted by treatment and overlaid with geometric mean. ARV-471 and ARV-473 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 versus time profiles will also be presented.

Natural log transformed ARV-471 and ARV-473 AUC_{inf} (if data permit), AUC_{last} and C_{max} 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% CIs for the ratios. Treatment A (ARV-471 given alone) is the Reference Treatment while Treatments B (ARV-471 given after multiple doses of itraconazole) is the Test Treatment.

Ethical Considerations:

Participants are not expected to receive any clinical benefit. Participants contribute to the process of developing a new therapy for the treatment of patients with ER+/HER2- breast cancer.

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: ARV-471 Alone

Visit Identifier Abbreviations used in this table may be found in Appendix 11.	**Screen**	**Period 1**							**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Period 1 Day 1). *: At PI discretion, participant are allowed to remain in CRU from D-1 Period 1 until D12 of Period 2. In that case, discharge assessments of Period 1 described below will not be performed.
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				Participants will be admitted to the CRU on the day prior to ARV-471 dosing (Day -1 of Period 1) and may be kept at the CRU through at least Day 4 of Period 1 at the discretion of the investigator. 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.
Outpatient Visit	X						X	X		Outpatient visit required only if participant is discharged on Day 4.
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.
Physical exam	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.
Blood pressure and pulse rate	X		X	X					X	Obtain supine BP and PR following at least a 5 minute rest in a supine position. Refer to Table 3 for BP and PR measurements.

Table 1. Period 1: ARV-471 Alone

Visit Identifier Abbreviations used in this table may be found in Appendix 11.	**Screen**	**Period 1**							**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Period 1 Day 1). *: At PI discretion, participant are allowed to remain in CRU from D-1 Period 1 until D12 of Period 2. In that case, discharge assessments of Period 1 described below will not be performed.
Safety laboratory	X	X				X		X*	X	Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed at the indicated time-points. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator. Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.
12-Lead ECG	X		X	X		X*			X	Refer to Table 3 for single 12-lead ECG collections.
Demography	X									Demographics will include participant, race, ethnicity, age, and gender during the screening visit.
Contraception check	X	X				X*	X*	X*	X	On Screening, Day -1 and on Day 4 (or any day that coincides with discharge), the investigator or their designee will discuss with the participant and their partner the need to use highly effective contraception consistently and correctly according to contraception guidelines. If participants are discharged on Day 4, the contraception check will be done at each outpatient visit.
FSH	X									Will be performed at screening for postmenopausal (amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause) female participants only.
Urine drug testing	X	X								Urine drug (mandatory) and alcohol breath and blood 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.
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		Performed according to CRU procedure.
ARV-471 administration			X							On Period 1 Day 1, participants will be given a high fat, high calorie meal at approximately 30 minutes prior to ARV-471 dosing. The high fat, high calorie breakfast will be consumed within a 20-minute period, with the study drug administered within approximately 10 minutes after completion of the meal. Administration of 200 mg ARV-471 will occur with approximately 240 mL of water followed by at least 4 hours fast post dosing. A washout period of at least 10 days must occur between the 2 successive single doses of ARV-471 in this study
Retained Research Samples 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.

Table 1. Period 1: ARV-471 Alone

Visit Identifier Abbreviations used in this table may be found in Appendix 11.	**Screen**	**Period 1**							**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Period 1 Day 1). *: At PI discretion, participant are allowed to remain in CRU from D-1 Period 1 until D12 of Period 2. In that case, discharge assessments of Period 1 described below will not be performed.
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 nonserious AE monitoring	X	→	→	→	→	→	→	X	X	See Section 8.4.3 for AE and SAE assessments.

Table 2. Period 2: ARV-471 in the Presence of Itraconazole

Visit Identifier Abbreviations used in this table may be found in Appendix 11.	**Period 2**					**F/U**	**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -1**	**Day 1-4**	**Day 5**	**Day 6-11**	**Day 12**	**28-35 Days**		• Day relative to start of study intervention (Period 2 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. *: At PI discretion, participant are allowed to remain in CRU from D-1 Period 1 until D12 of Period 2. In that case, admission assessment for Period 2 describe below will not be performed.
CRU confinement	X	→	→	→	X			Participants will be admitted to the CRU on the day prior to itraconazole dosing (Day -1) and will be kept at the CRU through Day 12 of Period 2 at the discretion of the investigator. 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.

Table 2. Period 2: ARV-471 in the Presence of Itraconazole

Visit Identifier Abbreviations used in this table may be found in Appendix 11.	**Period 2**					**F/U**	**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -1**	**Day 1-4**	**Day 5**	**Day 6-11**	**Day 12**	**28-35 Days**		• Day relative to start of study intervention (Period 2 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. *: At PI discretion, participant are allowed to remain in CRU from D-1 Period 1 until D12 of Period 2. In that case, admission assessment for Period 2 describe below will not be performed.
Blood pressure and pulse rate							X	Obtain supine BP and PR following at least a 5 minute rest in a supine position. Refer to Table 4 for BP and PR measurements.
Safety laboratory	X	X (Day 4 only)			X		X	Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed at the indicated time-points. Additional safety laboratory assessments may be performed at any time at the discretion of the investigator. Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.
12-Lead ECG			X	X (Day 6 only)	X		X	Refer to Table 4 for single 12-lead ECG collections.
Contraception check	X*				X		X	On Day -1, on Day 12 (or any day that coincides with discharge) and if participants discontinues early, the investigator or their designee will discuss with the participant and their partner the need to use highly effective contraception consistently and correctly according to contraception guidelines.
Urine drug testing	X*							Urine drug (mandatory) and alcohol breath and blood test (at discretion of investigator) will be performed at on Day -1. These tests may be performed at any other time at the discretion of the investigator.
COVID-19 related measures	X	X	X	X	X			Performed according to CRU procedure.
Itraconazole administration		X	X	X				Participants will receive itraconazole 200 mg (in a 20 mL solution) once daily while fasted with approximately 220 mL of water from Day 1 to Day 11. Itraconazole does not need to be administered under fasted conditions when taken with ARV-471 on Day 5.

Table 2. Period 2: ARV-471 in the Presence of Itraconazole

Visit Identifier Abbreviations used in this table may be found in Appendix 11.	**Period 2**					**F/U**	**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -1**	**Day 1-4**	**Day 5**	**Day 6-11**	**Day 12**	**28-35 Days**		• Day relative to start of study intervention (Period 2 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. *: At PI discretion, participant are allowed to remain in CRU from D-1 Period 1 until D12 of Period 2. In that case, admission assessment for Period 2 describe below will not be performed.
ARV-471 administration			X					On Period 2 Day 5, participants will be given a high fat, high calorie meal at approximately 30 minutes prior to ARV-471 dosing. The high fat, high calorie breakfast will be consumed within a 20-minute period, with the study drug administered within approximately 10 minutes after completion of the meal. Administration of 200 mg ARV-471 will occur with approximately 220 mL of water followed by at least 4 hours fast post dosing.
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 nonserious AE monitoring	→	→	→	→	X	X	X	See Section 8.4.3 for AE and SAE assessments.

Table 3. PK, ECG, BP, and PR Sampling Schema for Period 1

Visit Identifier	Screening	Study C4891009													Early Discontinuation	Notes
Study Day	**Day -28 to Day -2**	**1**								**2**	**3**	**4**	**5**	**6**		*: At PI discretion, participant are allowed to remain in CRU from D-1 Period 1 until D12 of Period 2. In that case, admission assessment for Period 2 describe below will not be performed.
Hours Before/After Dose		**Pre-dose**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**	**120**		
ARV-471/ARV-473 PK blood sampling[a]		X		X	X	X	X	X	X	X	X	X	X	X	X	a: Blood samples (3 mL) for PK analysis of ARV-471 will be taken after completion of ECGs, blood pressure and pulse rate at pre-dose (within 15 minutes prior to starting breakfast), 1 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours post dosing. If ECG and blood pressure/pulse rate assessments are scheduled at the same time point, PK samples should be collected after completion of these assessments.
12-Lead ECG	X	X (Triplicate ECG)					X		X	X		X*			X	Singlet 12-lead ECG readings approximately 2 minutes apart will be taken at specified times. Triplicate ECG will be collected at pre-dose on Day 1. All ECG assessments will be made after at least a 5-minute rest in a supine position and prior to any blood draws or vital sign measurements. See Section 8.3.3 for details.
Blood pressure and pulse rate	X	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 assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time. See Section 8.3.2 for details.

Table 4. PK, ECG, BP, and PR Sampling Schema for Period 2

Visit Identifier		Study C4891009															Early Discontinuation	Notes
Study Day	**1-4**	**5**							**6**	**7**	**8**	**9**	**10**	**11**	**12**			
Hours Before/After Dose		**Predose**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**	**120**	**144**	**168**		
ARV-471/ARV-473 PK blood sampling[a]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	a: Blood samples (3 mL) for PK analysis of ARV-471 will be taken after completion of ECGs, blood pressure and pulse rate at pre-dose (within 15 minutes prior to starting breakfast), 1 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 hours post dosing. If ECG and blood pressure/pulse rate assessments are scheduled at the same time point, PK samples should be collected after completion of these assessments.
12-Lead ECG		X (Triplicate ECG)					X		X	X						X	X	Single 12-lead ECG readings approximately 2 minutes apart will be taken at specified times. Triplicate ECG will be collected at pre-dose on Day 5. All ECG assessments will be made after at least a 5-minute rest in a supine position and prior to any blood draws or vital sign measurements.
Blood pressure and pulse rate		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 assessments will be performed after collection of ECGs and prior to collection of blood draws if scheduled at the same time.

2. INTRODUCTION

ARV-471 (also known as PF-07850327) is a potent, selective, orally bioavailable PROteolysis TArgeting Chimeric (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.

2.1. Study Rationale

Itraconazole and its primary metabolite (hydroxy-itraconazole) are specific strong inhibitors of CYP3A. Since ARV-471 is a substrate for CYP3A, concomitant administration of multiple doses of itraconazole along with ARV-471 may lead to increased systemic exposure of ARV-471. The objective of this study is to estimate the effect of multiple doses of itraconazole on the PK of ARV-471.

2.2. Background

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

2.2.1. Nonclinical Pharmacology

In nonclinical studies, ARV-471 demonstrated in vitro CCI (<CCI nM) and CCI (>CCI ER degradation even in the presence of clinically relevant, mutated (Y537S and D538G) forms of ER. Based on non-clinical studies, ARV-471 may have advantages over fulvestrant and other oral SERDs in clinical development such as RAD1901/elacestrant.[1] While SERDs destabilize ER and indirectly lead to ER degradation, ARV-471 actively degrades ER, which may lead to less drug resistance. In vivo, ARV-471 inhibits tumor growth in multiple mouse xenograft models. Notably, ARV-471 demonstrates superior TGI compared to fulvestrant in a Y537S ESR1 *mutant* patient-derived xenograft model (ARV-471 IB). 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

The PK profile of ARV-471 in the nonclinical species (mouse, rat, dog, and monkey) was characterized by a CCI clearance (CCI of hepatic blood flow), CCI tissue distribution CCI L/kg), CCI half-life of elimination ($t_{½}$)

CCI and CCI oral bioavailability CCI ARV-471 can interconvert to its epimer, ARV-473 (ARV-471 IB).

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

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.

A CYP reaction phenotyping study was conducted using 2 orthogonal methods in human liver microsomes and recombinant CYP isoforms. This study indicated CYP3A4 as the principal isoform responsible for CYP metabolism of ARV-471 (accounting for 85%). (ARV-471 IB)

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 (Version 4.0) and in 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 months (but not 1-month) ARV-471 administration in dogs. Changes in the CCI interval were only observed after CCI days of continuous dosing. No indication of CCI were observed in any study. There were no significant respiratory or CNS effects. ARV-471 and ARV-473 did not impact CCI CCI was initially assessed at the nominal concentration of CCI concentrations, respectively.

In a dedicated GLP cardiovascular assessment, a single dose of ARV-471 was administered via oral gavage to telemetered conscious male and female beagle dogs at doses of CCI and CCI mg/kg. No ARV-471-related effects were noted after oral administration of ARV-471 at 90 and 200 mg/kg. Following administration of ARV-471 at CCI mg/kg a CCI 7 ms CCI of the CCI was noted from CCI hours postdose. No other ARV-471 related effects were noted at CCI mg/kg. At CCI mg/kg (the only dose studied in the TK phase), dogs (n=8, males and females combined) achieved a mean of CCI ng/mL for C_{max}, CCI hours for T_{max}, and CCI ng•h/mL 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) assays, an 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 to CCI mg/kg/day. ARV-471-related CCI were considered related to the CCI and included changes in the 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 in the CCI were noted in rats in the 28-day study. No CCI have been noted in the dog toxicity studies up to 3-months in duration. Subsequently, in the 3-month study in rats there were CCI in the CCI. Based on the collective nonclinical data evaluating CCI of ARV-471 in rat and dog, it is concluded that the CCI observed only in the 1-month rat study was a spurious finding and not relevant to patients. The NOAEL for 3 months of oral dosing was determined to be the highest dose tested of CCI mg/kg/day in male rats. A NOAEL was not identified in female rats as the effects on the CCI were consider CCI. However, these findings are related to the primary pharmacology of ARV-471, CCI and CCI after CCI. At the CCI mg/kg/day dose level, the C_{max} was CCI ng/mL in males and females, respectively, and the AUC_{0-24} was CCI ng•h/mL in males and females, respectively.

ARV-471 was CCI in repeat dose dog studies up to 3-months in duration at doses up CCI mg/kg/day. ARV-471 produced changes in female and male CCI, consistent with CCI. The CCI mg/kg/day was identified as the NOAEL for daily dosing for 3 months in males. A NOAEL was not identified for females based upon microscopic findings in the CCI, CCI at ≥CCI mg/kg/day that were considered adverse, but it is acknowledged that these effects were consistent with the CCI of ARV-471 and were also observed in the 7- and 28-day studies in dogs. In males and females at CCI mg/kg/day, the C_{max} was CCI and CCI ng/mL and AUC_{0-24} was CCI ng•h/mL on Day 91, respectively.

2.2.4. Clinical Overview

In the ongoing FIH Study [ARV-471-mBC-101], ARV-471 is being assessed as a monotherapy and in combination with palbociclib in participants with ER+/HER2- aBC who had previously received CDK4/6 inhibitors and/or endocrine therapy and/or chemotherapy in the locally advanced/metastatic setting. The FIH study has 3 parts: Part A is a monotherapy dose escalation, Part B is a monotherapy dose expansion (200 mg or 500 mg, oral daily dosing), and Part C is evaluating the combination of ARV-471 and palbociclib (escalation and expansion). As of 06 June 2022, 176 participants have been treated in the FIH study (Part A n=78; Part B n=71, Part C n=27) (ARV-471 IB).

Based on the current safety data (data cutoff date of 06 June 2022), ARV-471 has been well-tolerated across total daily doses of 30 mg to 700 mg in patients with mBC, with no DLTs observed and most TRAE were Grade 1 or 2. In addition, evaluation of preliminary safety data from participants treated with palbociclib in combination with ARV-471 shows TEAEs consistent with TEAEs observed after treatment with either ARV-471 or palbociclib alone (ARV-471 IB).

Concentration-QTc modeling analysis of data from the ongoing ARV-471-mBC-101 study revealed a concentration-dependent increase in QTcF. Based on the model, a QTcF change from baseline is predicted to be [redacted] msec (90% CI: [redacted]) at the geometric mean C_{max} for the sum of ARV-471 and ARV-473 ([redacted] ng/mL) at steady-state after 200 mg QD dosing. Based on the categorical analysis of ECG data from 149 participants in Study 101 Part A and Part B (data cutoff date of 06 Jun 2022), 3 participants experienced a QTcF >[redacted] msec (1 of each at 180 mg, 200 mg, and 500 mg daily dose) and 4 participants had [redacted] from baseline >[redacted] msec (1 at 200 mg, 2 at 500 mg and 1 at 700 mg daily dose). From the ongoing ARV-471-mBC-101 study, as of 06 June 2022, 13 participants reported TEAEs of [redacted] (12 participants had TRAEs and in 1 participant the AE was considered as not related to ARV-471 per investigator). Most participants experienced grade 1 or 2 [redacted] events (11 out of 13), two patients reported Grade 3 events and no Grade 4/5 have been reported. An external [redacted] consultant review concluded that of the 13 participants who reported [redacted] events, only 2 participants had a true diagnosis of [redacted], of which [redacted] were confounding factors.

There have been [redacted] aths reported in the ARV-471-mBC-101 study: [redacted] in Part A and [redacted] in Part B. [redacted] of these [redacted] were attributable to ARV-471. [redacted] have been reported in Part C.

There was evidence of preliminary clinical activity in the Part A monotherapy dose escalation of Study ARV-471-mBC-101, with several patients achieving clinical benefit as defined by CBR as of 06 June 2022. CBR (rate of confirmed CR, PR, or SD ≥24 weeks) was 36.2% (95% CI: 25.0 - 48.7) in 25 of 69 evaluable participants. Clinical benefit (by CBR) was observed in CDK4/6 inhibitor-pretreated patients with ER+/HER2- BC in all Part A dose cohorts. Efficacy data collection is ongoing for Part B and Part C.

Preliminary PK data following single and multiple dosing from Part A monotherapy dose escalation of Study ARV-471-mBC-101 are available in mBC participants receiving ARV-471 at total daily dose levels ranging from 30 mg to 700 mg (administered either as QD or BID) under fed conditions. The median T_{max} ranged from [redacted] to [redacted] hours across the dose levels. The mean effective $t_{½}$ at steady state ranged from [redacted] hours. Clinical exposure of ARV-471 on Day 15 at 60 mg QD (geometric mean AUC_{tau} [redacted] ng.h/mL) has exceeded the nonclinical efficacious range associated with TGI (30 mg/kg single dose in mice). Following 200 mg QD dosing (N=8), a geometric mean accumulation ratio for AUC_{tau} of [redacted] was observed between Day 1 and Day 15. ARV-471 can interconvert to its epimer, ARV-473. Following 200 mg QD dosing (N=8), the ratio, based on AUC_{tau}, of ARV-473 / ARV-471 on Cycle 1 Day 15 i[redacted] reclinical data showed ARV-471 has both [redacted] and degradation activities against ER, whereas ARV-473 displays only [redacted] activity (ARV-471 IB).

Safety and PK data in healthy volunteers is based on the Phase 1 clinical pharmacology study, Study [redacted], which is evaluating the effect of food or a PPI (esomeprazole) and the rBA of different tablet formulations on the single-dose PK and safety of ARV-471 in healthy postmenopausal female volunteers. As of data cut-off date of 16 June

2022, a total of 47 healthy participants have been treated in Study CCI (14 participants in FE, 17 participants in PPI, and 16 participants in rBA portions). Each participant received 2 doses of 200 mg ARV-471, 1 in each of the 2 periods, and the ARV-471 treatments were separated by a washout period of at least 14 days. Preliminary analysis results showed the median T_{max} ranged from CCI hours across the cohorts. The geometric mean $t_{½}$ following a single 200 mg dose was about CCI hours under fed condition. Food intake CCI ARV-471 C_{max} and AUC_{inf} CCI fold, respectively, as compared with fasted conditions. Thus, patients should be instructed to take ARV-471 with food. ARV-471 AUC values were similar when administered with PPI or without PPI, although PPI CCI ARV-471 C_{max} about CCI which is not considered clinical CCI This indicates that there are CCI of PPI on exposure of ARV-471 when administered with a CCI -fat meal.

Analysis of 14 paired biopsies from patients treated in Part A (monotherapy dose escalation) at various doses of ARV-471 suggest CCI ER degradation (up to CCI decrease, with a median ER decrease of CCI [range: CCI across all doses up to 500 mg QD, regardless of ESR1 mutation status with no apparent relationship between dose or exposure and ER degradation in patients with wild-type or mutant ER.

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

2.3. Benefit/Risk Assessment

ARV-471 alone or in combination with itraconazole 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.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of itraconazole are provided in the EU SmPC, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Study Intervention(s) ARV-471	
CCI	CCI based on CCI to date as per Section 2.2.3. CCI modeling analysis revealed a 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 were confounding factors. Clinical safety not yet fully characterized.	Participants receive a single dose during Periods 1 and 2 with a washout of at least 10 days between administration of ARV-471 doses. Participants will be monitored for CCI changes with CCI at screening and during the study intervention period (Table 3 and Table 4). Participants at high risk of CCI as per EC #9 are excluded from participation in the study (see Section 5.2). Use of prescription or nonprescription medications, including vitamins, herbal and dietary supplements, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products are prohibited within 7 days prior to the first dose of study intervention, with the exception of moderate/potent CYP3A inducers which are prohibited within 14 days plust 5 half-lives 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Venous Embolism	Potential risk based on metastatic cancer setting and known class effect with CCI One Grade 3 related CCI case, 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 receive a single dose during Periods 1 and 2 with a washout of at least 10 days between administration of ARV-471 doses. Participants with a history of clinically significant CCI events are excluded from participation in the study as per EC #1 (see Section 5.2).
Study Intervention(s) Itraconazole		
Hepatotoxicity	Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death.	AEs, vital signs, ECGs, and clinical laboratory test results will be monitored on an ongoing basis. Instructions for managing potential cases of drug induced liver injury, should they occur, are provided in Appendix 6. Participants will be monitored for QT interval changes with ECG monitoring at screening and during the study intervention period (Table 3 and Table 4). Participants at high risk of QT prolongation as per EC #9 are excluded from participation in the study (see Section 5.2).
Cardiac Dysrhythmias	Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as cisapride, pimozide, methadone, or quinidine concomitantly with itraconazole and/or other CYP3A inhibitors.	
Cardiac Disease	Itraconazole has been associated with reports of congestive heart failure. In post-marketing experience, heart failure was more frequently reported in patients receiving a total daily dose of 400 mg although there were also cases reported among those receiving lower total daily doses.	

2.3.2. Benefit Assessment

Participants are not expected to receive any clinical benefit. Participants contribute to the process of developing a new therapy for the treatment of patients with ER+/HER2- breast cancer.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with ARV-471 are justified by the anticipated benefits that may be afforded in the future to patients with ER+HER- metastatic breast cancer.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	
• To estimate the effect of multiple doses of itraconazole on the pharmacokinetics of a single oral 200 mg dose of ARV-471.	**Primary:** • Plasma AUC_{inf} and C_{max} of ARV-471 and ARV-473, as data permits (AUC_{last} if AUC_{inf} cannot be estimated).
Secondary:	
• To estimate the effect of multiple doses of itraconazole on the pharmacokinetics of a single oral 200 mg dose of ARV-471.	• Plasma AUC_{last}, T_{max}, $t_{1/2}$, CL/F and Vz/F of ARV-471 and ARV-473, as data permits.
• To evaluate the safety and tolerability of a single oral 200 mg dose of ARV-471 administered to healthy participants in the absence and presence of multiple doses of itraconazole under fed conditions.	• Safety laboratory tests, physical examination, vital signs, electrocardiograms, concomitant medication and adverse event monitoring.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, 2-period fixed-sequence crossover study to estimate the effect of multiple doses of the strong CYP3A inhibitor, itraconazole, on ARV-471 and ARV-473 pharmacokinetics in healthy males, and females of nonchildbearing potential. A total of approximately 12 participants will be enrolled in the study. The study will consist of 2 periods; Period 1 = single dose of ARV-471 alone and Period 2 = multiple doses of itraconazole + single dose of ARV-471. Following Period 1, a washout period of at least 10 days must occur between the 2 single doses of ARV-471. Following administration of ARV-471 in each period, participants will undergo serial PK sampling. 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.

In Period 1 (ARV-471 alone), each participant will be admitted to the research unit on Day -1. Participants will be required to remain in the research unit for at least 4 days until completion of the 72-hour PK sampling on Day 4, after which participants may be eligible

for discharge. Two additional outpatient visits (Days 5 and 6) are required to complete the PK sampling for Period 1. Alternatively, participants may be kept in-house through Day 12 of Period 2 at the discretion of the investigator.

Participants will be required to return to the research unit to start Period 2 at least 1 day after collection of the last PK sample on Day 6 of Period 1 in order to have at least 10 days between the 2 successive doses of ARV-471, and 4 days of pre-treatment with itraconazole. Participants may be admitted to the research unit on or before Day -1 of Period 2 until completion of 168-hour PK sampling on Day 12 of Period 2, after which participants will be discharged. The total study duration for each participant will be at least 17 days.

On Period 1 Day 1, participants will be provided the recommended high fat, high calorie breakfast 30 minutes prior to administration of ARV-471. No food will be allowed for at least 4 hours post-dose. Each participant will undergo serial blood samplings at pre-dose (before breakfast) and 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after ARV-471 administration to determine plasma concentrations of ARV-471.

During Period 2 Day 1 through Day 11 (except Day 5 for ARV-471 administration), participants will receive an itraconazole oral solution dose of 200 mg once daily under fasted conditions. Itraconazole does not need to be administered under fasted conditions on Day 5. No food will be allowed for at least 1 hour post itraconazole dose.

On Period 2 Day 5, participants will be provided a high fat, high calorie breakfast 30 minutes prior to the concomitant administration of itraconazole and ARV-471. Itraconazole 200 mg, as 20 mL Sporanox 10 mg/mL oral solution will be administered first, immediately followed by two 100 mg tablets of ARV-471. The study drugs (itraconazole and ARV-471) should be administered with approximately 220 mL of ambient temperature water. No food will be allowed for at least 4 hours following ARV-471 administration. PK sampling will be followed up to 168 hours on Day 12 (the planned time points include pre-dose, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours).

Physical examinations, 12-lead ECG, vital sign measurements, and clinical laboratory tests will be conducted and adverse events will be monitored throughout the study to assess safety. A safety follow-up visit may be conducted at the discretion of the investigator.

ARV-471 will be supplied by Pfizer as 100 mg tablets. Itraconazole (Sporanox®) oral solution for this study will be sourced locally by the CRU.

4.2. Scientific Rationale for Study Design

Study Treatment and Dose Rationale for Itraconazole: Itraconazole and its primary metabolite (hydroxy-itraconazole) are specific strong inhibitors of CYP3A. For these characteristics, along with its safety profile, itraconazole has often been utilized as a perpetrator drug for CYP3A inhibition PK drug interaction studies.[3, 4, 5, 6] Since ARV-471 is a substrate for CYP3A, concomitant administration of multiple doses of itraconazole along with ARV-471 may lead to increased systemic exposure of ARV-471. This may require ARV-471 dose adjustment when it is utilized with medications that are strong

CYP3A inhibitors. The objective of this study is to estimate the effect of multiple doses of itraconazole on the PK of ARV-471.

Itraconazole 200 mg is a typical clinical dose that achieves adequate strong CYP3A inhibition.[7] PK data indicates that itraconazole 200 mg oral solution provides highest itraconazole and hydroxy-itraconazole (both of which inhibit CYP3A) plasma exposure with less PK variability, when compared to itraconazole 200 mg capsules given in either fed or fasted states.[7, 8,9,10] Though exposure is maximized under fasted conditions with the solution formulation, oral exposures of itraconazole and hydroxy-itraconazole achieves adequate CYP3A inhibition under fed conditions.[7]

Washout period: Following a single dose of 200 mg ARV-471 administered with a high-fat meal, ARV-471 geometric mean terminal half-life was approximately CCI hours. Thus, a CCI is considered adequate for the washout of the ARV-471 from plasma. During the study, plasma concentrations should typically have dropped to BLQ before administration of the next dose (ie, no residual concentrations from the prior period) to minimize the carryover from the previous treatment.

Rationale for study population

Healthy Adults

Singles doses of ARV-471 200 mg was well tolerated in a Phase 1, multi-part, open-label study to evaluate the effect of food or a proton-pump inhibitor (esomeprazole) and to evaluate the relative bioavailability of different tablet formulations in healthy post-menopausal female participants.

It is well acknowledged that protein degradation and resynthesis rates are equal in the steady state.[11] ER protein levels are regulated by the ubiquitin-proteosome system[12] and resynthesized to maintain proper ER levels. The $t_{½}$ of ER is 1-3 hours in the presence of estradiol or dimethyl sulfoxide.[13, 14] In vitro nonclinical pharmacology studies demonstrated that ARV-471-mediated ER degradation was CCI of ER following compound removal. Therefore, it is anticipated that ER will be rapidly CCI as systemic levels of ARV-471 decline in healthy participants after administration of single doses of ARV-471 in this study. Because washout of ARV-471 and CCI is anticipated within 28 days, the risk of long-term adverse effects from a single dose of 200 mg ARV-471 is considered low.

Females of Non-childbearing Potential

ARV-471 is known to cause CCI in the CCI rats and dogs and male dogs, which may be regarded as 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, CCI ARV-471 may cause CCI when administered to the CCI therefore CCI.

Males

Nonclinical toxicology studies are reviewed in Sections 2.2.1-2.2.3 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 mg/kg/day in rats and CCI mg/kg/day in dogs. Across the studies, there were CCI , or CCI

In all studies, the pharmacologic effects of ARV-471 were on the CCI affected 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 CCI in animals administered ≥CCI mg/kg/day. ARV-471-related CCI noted in recovery sacrifice males included CCI of the CCI and CCI , which correlated with CCI . These findings in CCI may have reflected the CCI after degradation of the ER, compared to the CCI . A contributing factor to the effects on the CCI CCI) in the 28-day toxicity studies is likely the male dog sexually maturity at the initiation of dosing (7-9 months old). The male specific findings were considered non-adverse and NOAEL of CCI mg/kg/day 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 at CCI mg/kg/day with CCI CCI in the 3-month toxicity study may be explained by the sexual maturity of the dogs at the initiation of dosing. The exposure margins for testicular toxicity in rat and dog toxicity studies are shown in Table 5.

Table 5. 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)	Total Predicted Margins with Itraconazole[a]		
				Low	Medium	High
Rat	7 days	300 (NOEL)	CCI			
Rat	28 days	100 (NOEL)				
Rat	91 days	300 (NOEL)				
Dog	7 days	120 (NOAEL)				
Dog	28 days	90 (NOAEL)				
Dog	91 days	90 (NOAEL)				

a. Total predicted margins with itraconazole were based on the geometric mean AUC_{inf} (CCI ng*h/mL) following a single 200 mg dose of ARV-471 administered with a high fat meal in Study CCI 3. Predicted AUCs were calculated from AUC_{inf} multiplied by an AUCR of CCI based on ARV-471 fm,CYP3A values of CCI for the low, medium, and high columns, respectively. AUCR values reflect the magnitude of the model-predicted effect of the strong CYP3A inhibitor, itraconazole.

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

While a single dose of ARV-471 may carry CCI of producing CCI based on the CCI of ARV-471, the risk of CCI There was no evidence of effects on CCI, confirming the CCI. Learnings from published literature support the position that male tissues would fully recover and there would not be a permanent effect on male fertility.[15] 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.[16, 17] 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.[16, 17] 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."[16] Meistrich et al also pointed out that these 2 drugs, thiotepa and adriamycin, are strong mutagens, CCI [redacted].[17]

In summary, given that the CCI [redacted] tested provided a CCI [redacted] based on estimated low, medium, and high ARV-471 exposure, respectively, when given with a strong inhibitor of CYP3A4, itraconazole in the 3-month toxicity study, the CCI [redacted] to spermatogenic activity in dogs shown in all studies to date, the CCI [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 CCI [redacted] is assessed to be CCI [redacted] when ARV-471 is administered as a single oral dose.

The current study will be conducted in healthy participants who will receive single oral doses of ARV-471 200 mg alone and concomitantly with itraconazole in the fed state with at least a 10 day washout period between ARV-471 doses. As indicated above, for a single oral 200 mg dose the CCI [redacted] provides a safety margin of CCI [redacted] fold based on estimated medium ARV-471 exposure with respect to the CCI [redacted] in the 3-month toxicity study recommended by ICH Guidance. Plasma exposure of ARV-471 is generally dose-proportional within the dose range of 30 to 500 mg QD in humans. Based on the expected increase in ARV-471 systemic exposure in the presence of itraconazole (estimated to be CCI [redacted]-fold increase for AUC following concomitant administration of a single 200 mg dose of ARV-471 with itraconazole compared to ARV-471 alone (Section 4.3), and assuming dose proportionality, then the extrapolated safety margin over the effect of male reproductive effects when a single 200 mg oral dose of ARV-471 is given with itraconazole is projected to be an acceptable fold safety margin. Exposure margins estimates are provided in Table 8 and Table 9 in Section 4.3 for rat and dog, respectively.

4.2.1. Choice of Contraception/Barrier Requirements

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

4.2.1.1. Females

Females 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).

4.2.1.2. 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.

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

A single dose of 200 mg ARV-471 has been tested in a Phase 1, multi-part, open-label study to evaluate the effect of food or a proton-pump inhibitor (esomeprazole) and to evaluate the relative bioavailability of different tablet ARV-471 formulations in healthy post-menopausal female participants. In the food effect part of the study, geometric mean AUC_{inf} and C_{max} ARV-471 CCI, respectively, when ARV-471 was administered with a high-fat, high caloric meal compared to under fasted conditions.

Multiple daily doses up to 700 mg ARV-471 have been shown to be safe and well tolerated in patients with mBC. Following multiple doses of 500 mg daily, geometric mean AUC_{tau} on Cycle 1 Day 15 was CCI ng*h/mL in CCI In the food effect portion of Study CCI, the geometric mean AUC_{inf} following a single dose of ARV-471 200 mg administered with a high fat meal was CCI ng*h/mL (n CCI) (Table 6). Using the in vitro-derived point estimate of ARV-471 $f_{m,CYP3A}$ of CCI, ARV-471 plasma exposure when administered under fed conditions with a high fat meal is estimated to be CCI ng*h/mL, which is CCI than AUC_{tau} observed for 500 mg daily dosing on Cycle 1 Day 15 in CCI.

Table 6. Summary of Plasma ARV-471 AUC_{inf} (h*ng/mL) by Treatment (Fed/Fasted) in Study CCI

	AUC_{inf} (h*ng/mL)	
	ARV-471 200 mg Fasted (N=CCI)	ARV-471 200 mg Fed (N=CCI)
n		
Mean		
SD		
CV%		
Median		
Minimum		
Maximum		
Geometric mean		
Geometric CV%		

Table 6. Summary of Plasma ARV-471 AUC_{inf} (h*ng/mL) by Treatment (Fed/Fasted) in Study [redacted]

Note: Geometric CV% = 100 × (exp[SD^2]-1)$^{0.5}$, where SD is the standard deviation of the logarithmic-transformed data.
AUC_{inf} = area under the plasma concentration-time curve from the time of dosing extrapolated to infinity

An in vitro study was conducted to provide a preliminary estimate of the fraction of ARV-471 metabolized by CYP3A ($f_{m,CYP3A}$). As metabolic turnover of ARV-471 is [redacted] in human in vitro metabolic systems, a [redacted] approach was utilized. [redacted] were used as the preferred in [redacted] system, as they are considered a [redacted].

The preliminary estimate of ARV-471 $f_{m,CYP3A}$ is [redacted] (ie, CYP3A accounts for [redacted] of the metabolic clearance of ARV-471).

The magnitude of the model-predicted effect of the strong CYP3A inhibitor itraconazole (200 mg QD; solution formulation, fasted state) on the PK of ARV-471, over a range of ARV-471 $f_{m,CYP3A}$ values of [redacted], is summarized in Table 7.

Table 7. Mechanistic static DDI model predictions of the effect of steady-state itraconazole (200 mg QD) on the PK of ARV-471

Prediction	Object Drug	$f_{m,CYP3A}$	AUC_R of Object Drug		
			Predicted	Observed	P/O
Point Estimate	ARV-471	[redacted]		--	--
Sensitivity Analysis (Low)	ARV-471			--	--
Sensitivity Analysis (High)	ARV-471			--	--
Positive Control	lorlatinib			[redacted]	[redacted]

Using the in vitro-derived point estimate of ARV-471 $f_{m,CYP3A}$ of [redacted] itraconazole is predicted to increase ARV-471 exposure by [redacted] (AUC_R = [redacted]). A sensitivity analysis of ARV-471 $f_{m,CYP3A}$ [redacted]) resulted in predicted increases in ARV-471 exposure ranging from [redacted] (AUC_R = [redacted]) (AUC_R = [redacted]), respectively. This prediction indicates that ARV-471 plasma exposures are not expected to be substantially increased (eg, [redacted]-fold) in the presence of a strong CYP3A inhibitor like itraconazole.

Exposure margins estimates are provided in Table 8 and Table 9 below for rat and dog, respectively.

In rats, [redacted] mg/kg/day was identified as the [redacted] for daily dosing for 3 months in males. A [redacted] for females based upon [redacted] in the female reproductive tract that were considered [redacted], however these findings were consistent with the [redacted] of ARV-471 and are expected to be [redacted] based on other toxicity studies with ARV-471. In dogs, [redacted] mg/kg/day was identified as the [redacted]

for daily dosing for 3 months in males. CCI for females based upon CCI in the CCI again attributed to the CCI of ARV-471. CCI were identified, and all findings are expected to be CCI.

The nonclinical toxicity assessments up to 3 months support the safety of ARV-471 and confirm the CCI with the key identified effects on CCI. The projected maximal AUC (CCI ng*h/mL) that may be achieved in the current clinical study was exceeded in both rats and dogs in the 3-month toxicity studies and was CCI with key findings associated with the pharmacological effects of ARV-471. The margins based on the fed state are CCI-CCI in rats and CCI in dogs based on estimated low, medium, and high ARV-471 exposure, respectively, when given with a strong inhibitor of CYP3A4, itraconazole. The nonclinical profile supports the administration of the proposed two dose regimen in study C4891009 and increased exposures in patients would be anticipated to be CCI.

Table 8. Repeat Dose Toxicity Study ARV-471 Exposure Margins in Male and Female Rats

Study	Male Rats					Female Rats				
	Dose, mg/kg/day	Total AUC[a], ng*h/mL	Total Predicted Margins with Itraconazole[b]			Dose, mg/kg/day	Total AUC[a], ng*h/mL	Total Predicted Margins with Itraconazole		
			Low	Medium	High			Low	Medium	High
7 Day	30	CCI				30	CCI			
7 Day	100					100				
7 Day	300					300				
28-Day	3					3				
28-Day	10					10				
28-Day	30					30				
28-Day	100[c]					100[c]				
3-Month	30					30				
3-Month	100					100[c]				
3-Month	300[c]					300				

a. Day last

b. Total predicted margins with itraconazole were based on the geometric mean AUCinf CCI ng*h/mL) following a single 200 mg dose of ARV-471 administered with a high fat meal in Study CCI. Predicted AUCs were calculated from AUCinf multiplied by an AUCR of CCI based on ARV-471 fm,CYP3A values of CCI, for the low, medium, and high columns, respectively. AUCR values reflect the magnitude of the model-predicted effect of the strong CYP3A inhibitor, itraconazole.

c. NOAEL

Table 9. Repeat Dose Toxicity Studies Exposure Margins in Male and Female Beagle Dogs

	Male Dogs					Female Dogs				
Study	**Dose, mg/kg/ day**	**Total AUC[a], ng*h/ mL**	**Total Predicted Margins with Itraconazole[b]**			**Dose, mg/kg/ day**	**Total AUC[a], ng*h/ mL**	**Total Predicted Margins with Itraconazole[b]**		
			Low	Medium	High			Low	Medium	High
7 Day	30	CCI				30	CCI			
7 Day	60					60				
7 Day	120					120				
28-Day	15					15				
28-Day	45					45				
28-Day	90[c]					90[c]				
3-Month	10					10				
3-Month	30					30				
3-Month	90[c]					90				

a. Day last

b. Total predicted margins with itraconazole were based on the geometric mean AUCinf (CCI ng*h/mL) following a single 200 mg dose of ARV-471 administered with a high fat meal in Study CCI . Predicted AUCs were calculated from AUCinf multiplied by an AUCR of CCI based on ARV-471 fm,CYP3A values of CCI for the low, medium, and high columns, respectively. AUCR values reflect the magnitude of the model-predicted effect of the strong CYP3A inhibitor, itraconazole.

c. NOAEL

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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 65 years, inclusive at the time of signing the ICD. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG or clinical laboratory tests. 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, bilateral salpingectomy, and/or bilateral oophorectomy;

    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 salpingectomy, bilateral oophorectomy and/or ovarian failure) will be considered to be of childbearing potential.
    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) participants.

Other Inclusion Criteria:

2. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg.

3. Evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, cerebrovascular, 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).

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

2. Pregnant female participants, breastfeeding female participants, female participants of childbearing potential. Male participants with partners currently pregnant; fertile male participants 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. 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:

4. Use of prescription or non-prescription medications, including vitamins, herbal and dietary supplements, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products within 7 days prior to the first dose of study intervention with the exception of:

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

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

Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

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 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; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

11. Renal impairment as defined by an eGFR<60 mL/min/1.73m^2. Based upon participant age at screening, eGFR is calculated using the recommended CKD-EPI formulas in Table 14 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events.

Other Exclusion Criteria:

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

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

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

15. Known hypersensitivity or previous adverse events associated with azole antifungals or any of the formulation components of ARV-471.

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

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

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

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

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

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to ARV-471 dose administration and itraconazole dose administration days in both Periods 1 and 2. Participants must also abstain from all food and drink (except water) at least 4 hours post ARV-471 dose on Period 1 Day 1 and Period 2 Day 5.

- Water will be permitted until 1 hour prior to ARV-471 administration on Period 1 Day 1 and Period 2 Day 5. Water may be consumed without restriction beginning 1 hour after ARV-471 administration on Period 1 Day 1 and Period 2 Day 5. There will be no water restrictions for itraconazole dosing.

- On Period 1 Day 1 and Period 2 Day 5, participants will be provided the recommended high fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800-1000 calories with 150, 250, and 500-600 calories from protein, carbohydrate and fat, respectively) breakfast 30 minutes prior to administration of ARV-471. This meal will be consumed within a 20-minute period, with study drug (ARV-471) administered with approximately 240 mL of ambient temperature water within approximately 10 minutes after completion of the meal.

- During Period 2 Day 1 through Day 11 (except Day 5 for ARV-471 dosing), participants should take itraconazole under fasted conditions at approximately the same time each day. Itraconazole does not need to be administered under fasted conditions on Day 5. No food will be allowed for at least 1 hour post itraconazole dose.

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

- Lunch will be provided at least 4 hours after dosing with ARV-471.

- Dinner will be provided approximately 9 to 10 hours after dosing with ARV-471.

- 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 screening and Day -1, 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.

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, 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 interventions refers to investigational product ARV-471 and itraconazole.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	ARV-471 (PF-07850327)	Itraconazole
Type	Drug	Drug
Dose Formulation	Tablet	Oral Solution
Unit Dose Strength(s)	100 mg	10 mg/mL
Dosage Level(s)	200 mg	200 mg
Route of Administration	Oral	Oral
Use	Experimental	Experimental treatment to assess an endpoint
IMP or NIMP/AxMP	IMP	NIMP/AxMP
Sourcing	Provided centrally by the sponsor	Sourced locally by the trial site

Study Intervention(s)		
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 dispensed into oral syringes
Current/Former Name(s) or Alias(es)	ARV-471 (PF-07850327)	Itraconazole (Sporanox®)

ARV-471 will be supplied to the CRU as a bulk supply in high-density polyethylene bottles with child-resistant caps and labelled according to local regulatory requirements. The bulk supply will be provided to the site for dispensing by the pharmacy. Itraconazole (Sporanox®) will be supplied locally by the CRU.

6.1.1. Administration

Period 1 Day 1: Following an overnight fast of least 10 hours and after the collection of the pre-dose ARV-471 PK sample, participants will start the recommended high fat, high-calorie breakfast consumed prior to administration of ARV-471, as two 100 mg tablets. Participants will receive study medication at approximately 0800 hours (plus or minus 2 hours). Investigator site personnel will administer study medication with ambient temperature water to a total volume of 240 mL. 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 Days 1-4 and 6-11: Following an overnight fast of at least 10 hours, participants will be administered 200 mg itraconazole (as 20 mL Sporanox 10 mg/mL oral solution) once daily under fasted conditions with approximately 220 mL of water. No food will be allowed for at least 1 hour post itraconazole dose.

Period 2 Day 5: Following an overnight fast of at least 10 hours and after the collection of the pre-dose ARV-471 PK sample, participants will start the recommended high fat, high-calorie breakfast consumed prior to the concomitant administration of itraconazole and ARV-471. Participants will receive study medications at approximately 0800 hours (plus or minus 2 hours). Itraconazole 200 mg, as 20 mL Sporanox 10 mg/mL oral solution will be administered first, immediately followed by the two 100 mg tablets of ARV-471. The study drugs (itraconazole and ARV-471) should be administered with approximately 220 mL of ambient temperature water. Participants will swallow the ARV-471 tablets 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 of both drugs.

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.

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 site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

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

ARV-471 tablets will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Commercial itraconazole (Sporanox ®) oral solution will be dispensed at the CRU into oral syringes 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) as allowed by local, state, and institutional guidance and labeled in accordance with Pfizer regulations and the investigator 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 other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

Dose modification is not permitted during the study.

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

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

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

There is no specific treatment for an overdose

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

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate 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 2 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Use of prescription or non-prescription medications, including vitamins, herbal and dietary supplements, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products within 7 days prior to the first dose of study intervention with the exception of:

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

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

Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

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 or itraconazole; 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

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. 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. Study treatment may continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Unacceptable toxicity;

- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

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 125 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. Screening 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).
- Collect height and weight as part of physical examination to obtain BMI for eligibility criteria.
- Obtain medical history, including but not limited to history of 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. 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 (urinalysis, hematology, and chemistry);
    - 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 Requirements and Concomitant Treatment(s) sections of the protocol.

8.2. Efficacy Assessments

Efficacy is not evaluated in this study.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

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

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

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

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

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

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

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

8.3.3. 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. At pre-dose on Period 1 Day 1 and Period 2 Day 5, triplicate 12 lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at each nominal time point and will serve as each participant's time controlled baseline QTcF value. Single ECGs will be collected for all other timepoints.

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

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

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

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

8.3.4. Clinical Safety Laboratory Assessments

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

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

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

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

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

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

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

8.3.5. COVID-19 Specific Assessments

Participants will undergo COVID-19 related measures per CRU procedures.

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

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the

event meets the criteria for classification as an SAE or caused the participant to discontinue the study (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 the 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 8.4.1.

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

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not Applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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

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

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

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of ARV-471 and ARV-473

Whole blood samples of approximately 3 mL, to provide a minimum of 1 mL plasma, will be collected for measurement of plasma concentrations of ARV-471 and ARV-473 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

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

Samples will be used to evaluate the PK of ARV-471 and ARV-473. Each plasma sample will be divided into 2 aliquots for PK analyses (one aliquot to be shipped, the other aliquot to remain at the site as a backup sample). Samples collected for analyses of ARV-471 and ARV-473 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples collected for measurement of plasma concentrations of ARV-471 and ARV-473 will be analyzed using a validated analytical method in compliance with applicable SOPs.

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

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5.2. Derivation of Pharmacokinetic Parameters

PK parameters, as appropriate, will be derived from the ARV-471 and ARV-473 concentration-time profiles as described in Table 10.

Table 10. Definitions of PK Parameters

Parameter[a]	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear-log trapezoidal method.
AUC_{inf}	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$. where C_{last} is the predicted plasma concentration at the last quantifiable time point and k_{el} is the elimination rate constant estimated from the log-linear regression analysis.
C_{max}	Maximum plasma concentration	Observed directly from the data.
T_{max}	Time for C_{max}	Observed directly from the data as time of first occurrence.

Table 10. Definitions of PK Parameters

Parameter[a]	Definition	Method of Determination
$t_{1/2}$	Terminal plasma elimination half-life	$Log_e(2)/k_{el}$ Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F	Apparent clearance after oral dose	$Dose/AUC_{inf}$ after oral dose.
V_z/F	Apparent volume of distribution after oral dose	$Dose/(AUC_{inf}*k_{el})$ after oral dose.
C_{last}	Last measurable observed concentration	Observed directly from the data
T_{last}	The time for C_{last}	Observed directly from the data

a. As data permit.

Actual PK sampling times will be used in the derivation of PK parameters whenever possible. In the case that actual PK sampling times are not available, nominal PK sampling time may be used in the derivation of PK parameters.

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. Specified Gene Expression (RNA) Research

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

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.4. Retained Research Samples for Biomarkers

Not applicable.

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 Hypothesis

No statistical hypothesis will be tested in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety Analysis Set	All participants enrolled and who take at least 1 dose of study intervention.
PK Concentration Analysis Set	All participants who are in the Safety Analysis Set and have at least 1 measurable ARV-471 or ARV-473 concentration.

Participant Analysis Set	Description
PK Parameter Analysis Set	All participants who are in the Safety Analysis Set and have at least 1 of the ARV-471 or ARV-473 PK parameters of primary interest.

9.3. Statistical Analyses

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

9.3.1. Pharmacokinetic Analyses

ARV-471 and ARV-473 PK parameters following a single dose administration of ARV-471 will be derived from the ARV-471 and ARV-473 plasma concentration versus time profiles using non-compartmental methods as data permit. The PK parameters to be assessed in this study, their definition, and method of determination are outlined in Table 10. ARV-471 and ARV-473 PK parameters (primary endpoints: AUC_{inf}, and C_{max}; Secondary endpoints:AUC_{last}, T_{max}, $t_{1/2}$, CL/F, and V_z/F) will be summarized descriptively by treatment. Individual participant parameters for AUC_{inf}, AUC_{last} and C_{max} will be plotted by treatment and overlaid with geometric mean. ARV-471 and ARV-473 concentrations will be listed and summarized descriptively by PK sampling time and treatment. Summary profiles (means and medians) of concentration time data will be plotted by treatment on linear and semi log scale. Individual participant concentration time profiles will also be presented. For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

Natural log transformed ARV-471 and ARV-473 AUC_{inf} (if data permit), AUC_{last} and C_{max} 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% CIs for the ratios. Treatment A (ARV-471 given alone) is the Reference Treatment while Treatments B (ARV-471 given after multiple doses of itraconazole) is the Test Treatment.

9.3.2. Safety Analyses

All safety analyses will be performed on the safety population.

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

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

9.3.2.1. Electrocardiogram Analyses

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

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

Table 11. 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 predose triplicate values on Day 1.

9.3.3. 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 reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

9.5. Sample Size Determination

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

The sample size is empirically selected and is not based on statistical power calculation.

A sample size of 12 PK evaluable participants who have at least 1 of the ARV-471/ARV-473 PK parameters of primary interest (AUC_{inf} or C_{max}) is expected to provide 90% CIs for the difference between treatments of CCI on the natural log scale for AUC_{inf} and C_{max}, respectively, with 80% coverage probability. Table 12 presents the width of 90% CI for different estimated effects. Sample size was based on ARV-471 only.

Table 12. Confidence Interval Estimation of PK Endpoints for Bioavailability

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf}	100% 110% 120% 130% 150%	CCI	
C_{max}	100% 110% 120% 130% 150%		

These calculations are based on estimates of within-participant standard deviation of CCI ARV-471 for $\log_e AUC_{inf}$ and $\log_e C_{max}$, respectively, based on the results from crossover study CCI.

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 theirpersonal 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 and monitoring 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, (c) and 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 13. 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 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	<u>Local dipstick</u> pH[a] Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin <u>Laboratory:</u> Microscopy and culture[b]	• COVID-19 testing (per CRU procedures) • Urine drug screening[c] • Alcohol breath and blood test (at discretion of investigator) <u>At screening:</u> • FSH[d] • Hepatitis B surface antigen • Hepatitis C antibody • HIV • Hepatitis B surface antibody • Hepatitis B core antibody

a. May be performed using local dipstick or pH-meter device.
b. Urinary culture only if deemed appropriate by the investigator (eg, Only if UTI is suspected and/or and urine dipstick is positive for nitrites or leukocyte esterase or both)
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. For confirmation of postmenopausal status only.

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

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

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

10.3.1. Definition of AE

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

Events <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 followup 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 (ARV-471), 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) 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 CCI 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

Table 14. Adults (18 Years and Above)—2021 CKD-EPI

2021 CKD-EPI Equations Scr[18] Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

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

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

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

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

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

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9: Overview of GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Table 15. Overview of GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Study **title/code**	**Date of completion of the Final Report**	**Test facility/test site in which the study was conducted (name and complete address)**	**Period in which the test facility/test site was used**	**Was the test facility/test site in that period part of an EU or an OECD MAD accepted GLP monitoring programme? (Y/N)**
[redacted]	[redacted]	CCI	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15. Overview of GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Study title/code	Date of completion of the Final Report	Test facility/test site in which the study was conducted (name and complete address)	Period in which the test facility/test site was used	Was the test facility/test site in that period part of an EU or an OECD MAD accepted GLP monitoring programme? (Y/N)
[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 16. Facilities for GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Facility	Inspection Date	Documents provided
CCI [redacted]	[redacted]	[redacted]

Table 16. Facilities for GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)

Facility	Inspection Date	Documents provided
CCI		

10.10. Appendix 10: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1.3. Schedule of Activities Table 2. Period 2: ARV-471 in the Presence of Itraconazole	Contraception check on Period 2 Day 4 was removed.	Contraception check at Period 2 Day 4 is not required since participants will be confined throughout the duration of Period 2 (Day -1 through Day 12) and contraception checks will occur Day -1 and Day 12.	Nonsubstantial
1.3. Schedule of Activities Table 1. Period 1: ARV-471 Alone	Table reformatted for contraception checks with a note added that "If participants are discharged on Day 4, the contraception check will be done at each outpatient visit."	Added for clarity since participants can be discharged on Period 1 Day 4.	Nonsubstantial
5.1. Inclusion Criteria	Added bilateral salpingectomy as a criteria that meets the definition for female participants of non-childbearing potential	Text added to align with Appendix 4 Section 10.4.3 Woman of Childbearing Potential	Nonsubstantial
Section 4.3. Justification for Dose	Content and tables were added to include exposure margin estimates for rat and dog.	Added content provide additional information on worst case scenario in terms of nonclinical safety.	Nonsubstantial
10.9. Appendix 9: Overview of GLP Safety Pharmacology and Toxicology Testing Program for ARV-471 (PF-07850327)	Tables were added for an overview of ARV-471 GLP safety pharmacology and toxicology testing program.	A summary table was provided specifying the details of the GLP studies and the facilities they were conducted at.	Nonsubstantial
1.3. Schedule of Activities Table 1. Period 1: ARV-471 Alone	Table reformatted to move 12-Lead ECG from Day 6 to Day 4 in Period 1.	Change made to be consistent with discharge on Period 1 Day 4.	Nonsubstantial
1.3. Schedule of Activities Table 3. PK, ECG, BP, and PR Sampling	Table reformatted to move 12-Lead ECG from Day 6 to Day 4 in Period 1.	Change made to be consistent with discharge on Period 1 Day 4.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Schema for Period 1			
4.2. Scientific Rationale for Study Design - Males	Section was revised with new data.	New data from the 3-month dog study provide further support for inclusion of male participants.	Nonsubstantial
1.1. Synopsis Objectives and Endpoints	Added "(AUClast if AUCinf cannot be estimated)."	Detail added to specify the action taken in the event that one of the primary PK endpoints cannot be estimated.	Nonsubstantial
3. OBJECTIVES AND ENDPOINTS	Added "(AUClast if AUCinf cannot be estimated)."	Detail added to specify the action taken in the event that one of the primary PK endpoints cannot be estimated.	Nonsubstantial
2.3. Benefit/Risk Assessment	EU SmPC has been added as the SRSD for itraconazole	SRSD for interacting drug was not stated in the original protocol.	Nonsubstantial
1.1. Synopsis Exclusion Criteria	“male participants of childbearing potential” has been replaced with “fertile male participants”	Changed to improve clarity and avoid confusion with the term "women of nonchildbearing potential".	Nonsubstantial
5.2. Exclusion Criteria	“male participants of childbearing potential” has been replaced with “fertile male participants”	Changed to improve clarity and avoid confusion with the term "women of nonchildbearing potential".	Nonsubstantial
2.2.1. Nonclinical Pharmacology	Revised background information	Revision made to align with updated IB.	Nonsubstantial
2.2.2. Nonclinical Pharmacokinetics and Metabolism	Revised background information	Revision made to align with updated IB.	Nonsubstantial
2.2.3. Nonclinical Safety	Revised background information	Revision made to align with updated IB and include new data.	Nonsubstantial
2.2.4. Clinical Overview	Revised background information	Revision made to align with updated IB.	Nonsubstantial
2.3.1. Risk Assessment	Revised background information	Revision made to align with updated IB.	Nonsubstantial
8.3.5. COVID-19 Specific Assessments	Section revised to “Participants will undergo COVID-19 related measures per CRU procedures.”	Language updated to allow for flexibility around COVID-19 assessments as rules continually change at the CRU.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
1.1. Synopsis Objectives and Endpoints	Added "200 mg" to dose	Added detail about dosing regimen.	Nonsubstantial
3. OBJECTIVES AND ENDPOINTS	Added "200 mg" to dose	Added detail about dosing regimen.	Nonsubstantial
4.2.1.2. Males	Added “(ARV-471)” to distinguish from itraconazole when investigational product is referred to.	Detail added for clarity	Nonsubstantial
10.4.1. Male Participant Reproductive Inclusion Criteria	Added “(ARV-471)” to distinguish from itraconazole when investigational product is referred to.	Detail added for clarity	Nonsubstantial
1.1. Synopsis Protocol Title	"Ar" changed to "ARV"	Drug name error.	Nonsubstantial
10.2. Appendix 2: Clinical Laboratory Tests	One bullet point was separated into two bullet points.	Formatting error.	Nonsubstantial
Title Page EudraCT Number	Number changed.	New EU CT Number assigned following resubmission of application.	Nonsubstantial

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
Abs	absolute
aBC	advanced Breast Cancer
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
AST	aspartate aminotransferase
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC_{last}	area under the plasma concentration time profile from time zero to the time of the last quantifiable concentration
AUC_R	ratio of the AUC of the object drug co-administered with itraconazole to the AUC of the object administered alone
AUC_{tau}	rea under plasma concentration-time curve over dosing interval
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
BID	twice a day
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CBR	clinical benefit rate
CDK	cyclin dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL/F	apparent clearance after oral dose
C_{last}	last quantifiable plasma concentration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)

Abbreviation	Term
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CV	cardiovascular
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
ER	estrogen receptor
eSAE	electronic serious adverse event
ESR	erythrocyte sedimentation rate
ET	endocrine therapy
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FE	food effect
FIH	first in human
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HER2	human epidermal growth factor receptor 2

Abbreviation	Term
hERG	human ether-a-go-go related gene
HHEP	human hepatocytes
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
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)
LBBB	left bundle branch block
LD_{50}	lethal dose 50%
LFT	liver function test
MAD	mutal acceptance of data
mBC	metastatic breast cancer
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MQI	medically qualified individual
N/A	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OECD	Organization for Economic Co-operation and Development
PCR	polymerase chain reaction
PCRU	Pfizer Clinical Research Unit
PE	physical exam
PK	pharmacokinetic(s)
P/O	predicted / observed
PPI	proton pump inhibitors
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
QD	once a day

Abbreviation	Term
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
rBA	relative bioavailability
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
Scr	serum creatinine
Scys	serum cystatin C
SD	stable disease
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulator
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal elimination half-life
T bili	total bilirubin
TEAE	treatment emergent adverse event
TGI	tumor growth inhibition
THC	tetrahydrocannabinol
TK	toxicokinetic(s)
T_{last}	the time for C_{last}
T_{max}	the time for C_{max}
TOC	table of contents
TRAE	treatment related adverse event
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
VE	Venous Embolism
V_z/F	apparent volume of distribution after oral dose
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

1. Flanagan J, Qian Y, Gough S, et al. Abstract P4-04-04: Identification and development of oral estrogen receptor PROTAC degraders for breast cancer. Cancer Research. 2018;78(4_Supplement):P4-04-04-P4-04-04.

2. Hamilton E, Vahdat L, Han HS, et al. Abstract PD13-08: First-in-human safety and activity of ARV-471, a novel PROTAC® estrogen receptor degrader, in ER+/HER2- locally advanced or metastatic breast cancer. Cancer Research. 2022;82(4_Supplement):PD13-08-PD13-08.

3. Backman JT, Kivisto KT, Olkkola KT, & Neuvonen PJ (1998) The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. European journal of clinical pharmacology 54(1):53-58.

4. Neuvonen PJ, Varhe A, & Olkkola KT (1996) The effect of ingestion time interval on the interaction between itraconazole and triazolam. Clinical Pharmacology & Therapeutics 60(3):326-331.

5. Olkkola KT, Ahonen J, & Neuvonen PJ (1996) The Effect of the Systemic Antimycotics, Itraconazole and Fluconazole, on the Pharmacokinetics and Pharmacodynamics of Intravenous and Oral Midazolam. Anesthesia & Analgesia 82(3).

6. Templeton I, Peng CC, Thummel KE et al. (2010) Accurate Prediction of Dose-Dependent CYP3A4 Inhibition by Itraconazole and Its Metabolites From In Vitro Inhibition Data. Clinical Pharmacology & Therapeutics 88(4):499-505.

7. Liu L, Bello A, Dresser MJ, et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. *J Clin Pharmacol*. 2016;56(2):143-151.

8. Barone JA, Moskovitz BL, Guarnieri J, et al. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. *Pharmacotherapy*. 1998; 18(2):295–301.

9. SPORANOX – itraconzole solution label. Raritan, NJ: JANSSEN_Pharmaceuticals; 2014.

10. SPORANOX – itraconzole capsule label. Raritan, NJ: JANSSEN_Pharmaceuticals; 2012.

11. Chou CJ, Affolter M, Kussmann M. A nutrigenomics view of protein intake: macronutrient, bioactive peptides, and protein turnover. Progress in Molecular Biology and Translational Science. 2012 Jan 1;108:51-74.

12. Nawaz Z, Lonard DM, Dennis AP, et al. Proteasome-dependent degradation of the human estrogen receptor. Proceedings of the National Academy of Sciences. 1999 Mar 2;96(5):1858-62.

13. Dauvois S, Danielian PS, White R, et al. Antiestrogen ICI 164,384 reduces cellular estrogen receptor content by increasing its turnover. Proceedings of the National Academy of Sciences. 1992 May 1;89(9):4037-41.

14. Weir HM, Bradbury RH, Lawson M, et al. AZD9496: an oral estrogen receptor inhibitor that blocks the growth of ER-positive and ESR1-mutant breast tumors in preclinical models. Cancer Research. 2016 Jun 1;76(11):3307-18.

15. Steinbach, TJ, Patrick, DJ, Cosenza, ME (Eds.). (2019). Toxicologic pathology for non-pathologists. Springer New York.

16. Lu, C.C. and M.L. Meistrich, Cytotoxic effects of chemotherapeutic drugs on mouse testis cells. Cancer Res, 1979. 39(9): p. 3575-82.

17. Meistrich, M.L., Finch M, da Cunha MF et al., Damaging effects of fourteen chemotherapeutic drugs on mouse testis cells. Cancer Res, 1982. 42(1): p. 122-31.

18. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med. 2021;385:1737-49.