Title Page

A PHASE I, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF ARV-471 (PF-07850327), A SINGLE AGENT IN JAPANESE PARTICIPANTS WITH ER+/HER2-LOCALLY ADVANCED OR METASTATIC BREAST CANCER

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Brief Title: Phase 1 Safety, Tolerability and Pharmacokinetics Study With ARV-471 (PF-07850327) in Japanese Participants With ER+/HER2- Locally Advanced or Metastatic BC

Document History

Document	Version Date
Amendment 2	21 Oct 2022
Amendment 1	25 Mar 2022
Original protocol	09 Feb 2022

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

Protocol Amendment Summary of Changes Table

Amendment 2 (21-October-2022)

Overall Rationale for the Amendment: The protocol was amended mainly to incorporate newly available data following the Investigator Brochure (v. 4.0) update.

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
2.2.4. Clinical Overview of ARV-471 2.3. Benefit/Risk Assessment	Updated the safety, PK and efficacy of ARV-471 in participants with locally advanced or metastatic ER+HER2- breast cancer in Study ARV-471-mBC-101 and in healthy volunteers in ARV-471-CPhm-103	To align with updated IB	Substantial
1.2. Schema 2.2.5. Rationale of dose selection in Phase 1 study in Japan 4.1. Overall Design 4.3. Justification for Dose 6.1. Study Intervention(s) Administered	Updated the starting dose to 200 mg QD based on the data from Part B in Study ARV-471-mBC-101	To align with the RP3D of ARV-471	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
6.5.1. Dose Interruption/Reductions 9.3.2. Primary Endpoint(s)/Estimand(s)/Analysis 9.5. Sample Size Determination			
5.2. Exclusion Criteria Exclusion Criteria 6 6.8.2. Proton Pump Inhibitors 10.8. Appendix 8: Prohibited Concomitant Medications That May Result in DDI	Updated the prohibited drugs	To align with updated IB	Substantial
5.3.2. Other Considerations	Deleted the Other Considerations	To align with updated IB	Substantial
1.3. Schedules of Activities Table 1 and Table 2	Corrected the visit window on Day 1 of Cycle 2 and beyond in Table 1 and at Cycle 2 and 3 Day 1 in Table 2	To incorporate changes/clarifications specified in the PACL (24 Jun 2022)	Non-substantial
6.4. Study Intervention Compliance	Updated not to be mandatory to retrieve the investigational drugs at every visit	To incorporate changes/clarifications specified in the PACL (24 Jun 2022)	Non-substantial
8.2.6. Pregnancy Testing 10.9.3.1. Laboratory Testing	Removed the reference to collection of the pregnancy test result on the CRF	To incorporate changes/clarifications specified in the PACL (24 Jun 2022)	Non-substantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Phase 1 Safety, Tolerability and Pharmacokinetics Study With ARV-471 (PF-07850327) in Japanese Participants With ER+/HER2- Locally Advanced or Metastatic BC

Rationale

ARV-471 is a PROteolysis-TArgeting Chimera (PROTAC®) hetero-bifunctional small molecule that induces active degradation of ER. ARV-471 is being developed for the treatment of patients with ER+/HER2- locally advanced or mBC. ARV-471 works by recruiting an E3 ligase to ubiquitinate ER which results in its subsequent degradation through the proteasome, a large, multi-subunit protein complex that degrades ubiquitinated proteins into small peptides. Such "active" degradation results in improved knockdown of tumor ER relative to fulvestrant in xenograft mouse models and produces TGI in vivo both as a single agent and in combination with palbociclib. Unlike fulvestrant, which is administered via IM injections, ARV-471 is orally administered. Further, in early preclinical studies, ARV-471 has demonstrated greater ER degradation compared to other oral SERDs in clinical development, such as AZD9496 and RAD1901[1].

Currently, ARV-471 is being evaluated in one Phase 1/2 study (Study ARV-471-mBC-101). The study is an FIH, open-label, 2-part, sequential group, 3+3 dose escalation (Part A), and cohort expansion (Part B) of single agent ARV-471 and a Phase 1b investigation of ARV-471 in combination with palbociclib to evaluate the safety and tolerability of ARV-471 (Part C), either as a single agent or in combination with palbociclib, in participants with locally advanced or mBC. The study will also characterize the first dose and steady-state PK profile, assess preliminary antitumor activity, PD effects on exploratory biomarkers and the safety of ARV-471 at the RP2D.

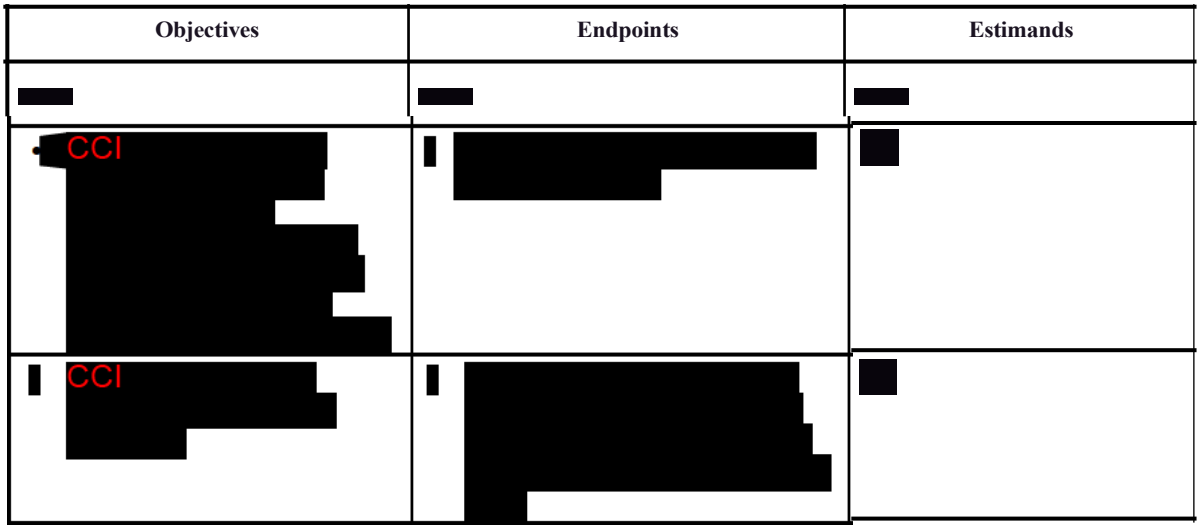
As of 06 June 2022, 78 participants have been treated in Part A in Study ARV-471-mBC-101. No DLTs have been reported and MTD has not been reached with ARV-471 monotherapy across total daily doses of 30 mg to 700 mg. The majority of TRAEs are Grade 1 or 2 in severity, with TRAEs in ≥10% of participants limited to nausea (25.6%), fatigue (21.8%), constipation (12.8%), arthralgia, decreased appetite, hot flush, and vomiting (10.3% each). Four participants experienced 6 Grade 3 TRAEs; headache lasting 1 day, asymptomatic amylase increased and lipase increased, nausea and asymptomatic ECG QT prolongation, and venous embolism that occurred after a minor procedure (bone biopsy). The participant with Grade 3 venous embolism was the only participant who discontinued ARV-471 due to a TRAE. In addition, evidence of clinical benefit has been observed in this heavily treated population, with a 36.2% CBR among 25 of 69 evaluable participants and a 8.6% ORR with 5 of 58 response-evaluable participants having confirmed PRs in Part A.

The purpose of this study is to confirm safety and tolerability at the RP3D of ARV-471 in Japanese participants with ER+/HER2- locally advanced or mBC. Since no DLTs had been reported across 30 mg to 700 mg total daily doses in Part A in Study ARV-471-mBC-101

and 200 mg QD was selected as the RP3D of ARV-471 from Part B, it is considered adequate to evaluate safety and tolerability at the RP3D, 200 mg QD in Phase 1 study in Japanese participants.

Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To evaluate the safety and tolerability of ARV-471 at the RP3D	First cycle DLTs	The primary estimand for incidence of DLTs is DLT rate estimated based on data from DLT-evaluable participants during the DLT evaluation period which is the first cycle of treatment (ie, 28 days) after the first dose of study intervention.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the overall safety profile	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing	NA
• To characterize the single-dose and multiple-dose PK of ARV-471 and ARV-473 (an epimer of ARV-471)	The following PK parameters will be assessed when applicable after a single dose and after multiple doses: single dose: AUC_{tau}, AUC_{last}, C_{max}, T_{max}, $t_{½}$, MRC_{max}, and $MRAUC_{tau}$ multiple doses; AUC_{tau}, AUC_{last}, C_{max}, C_{min}, C_{trough}, CL/F*, T_{max}, V_z/F*, R_{ac}, $t_{½}$, $t_{½eff}$, MRC_{max}, and $MRAUC_{tau}$ * ARV-471 only V_z/F and $t_{½}$ for single dose and multiple doses will be calculated only if data permit.	NA
• To explore preliminary antitumor activity	Antitumor activity of ARV-471 will be assessed by evaluating the following: • ORR per RECIST version 1.1 • CBR based on the summation of CRs, PRs and SD of 24 weeks duration or longer • Time to event endpoints: PFS, DOR	NA



Overall Design

Brief Summary

This study is a single-countiy, non-randomized, open-label, Phase 1 study. This study will evaluate the safety, tolerability, PK, and preliminary efficacy of ARV-471 as monotherapy in Japanese paiiicipants with ER+/HER2- locally advanced or mBC.

One dose level of ARV-471, 200 mg QD which has been detennined as the RP3D for monotherapy in the FIH study (Study ARV-471-mBC-101) conducted outside Japan, will be investigated. Six pa1iicipants will receive ARV-471 at 200 mg QD. If none or **1** pa1iicipant experience DLT during the first cycle (1 Cycle= 28 days), ARV-471, 200 mg QD will be considered tolerable as monotherapy in Japanese participants. lf2 participants experience DLT, the investigator and the sponsor should discuss the safety and tolerability based on the available data, and then under the agreement between the investigator and the sponsor, an additional 3 paiiicipants at the same dose level, up to a total of 9 paiiicipants, will be emolled to fmiher investigate the safety and tolerability of ARV-471 as monotherapy in Japanese paiiicipants. If no DLT is reported in an additional 3 participants, 200 mg QD will be considered tolerable in Japanese pa1iicipants. IfDLT is observed in 33% of pa1iicipants at 200 mg QD, the investigation at the next lower dose level may be explored.

Number of Participants

Six paiiicipants will be emolled to evaluate DLT and an additional 3 paiiicipants may be emolled depending on the number of paiiicipants with DLTs (total up to 9 paiiicipants). Paiiicipants who fail to complete at least 75% of study dmg ti·eatinent in Cycle 1 for reasons other than DLT are considered not to be DLT-evaluable and will be replaced. If 2 DLTs occur in 6 paiiicipants, the investigator and the sponsor should discuss the safety and tolerability based on the available data, and then under the agreement between the investigator and the sponsor, it may be allowed to emoll an additional 3 paiticipants at the

same dose level. Thus, the actual sample size may depend on the underlying dose toxicity profile.

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

Study Population and Specific Inclusion/Exclusion Criteria

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

Age and Sex:

1. Participants (women and men) at least 20 years of age at the time of signing the informed consent.

    - Postmenopausal women due to surgical or natural menopause, defined by **at least 1** of the following criteria:

        - Age ≥60 years.

        - Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; **and** follicle-stimulating hormone level within the laboratory's reference range for postmenopausal females.

        - Documented bilateral oophorectomy with surgery at least 2 months prior to start of study treatment.

        - Medically confirmed ovarian failure.

    - Pre- or perimenopausal women or men may be enrolled if treated with a GnRH analogue for at least 4 weeks prior to Cycle 1 Day 1. If a participant has received GnRH analogue, they must remain on it for the duration of the trial.

    - Refer to Section 10.4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Histological or cytological diagnosis of ER+/HER2- advanced breast cancer that is metastatic, recurrent, or locally advanced unresectable breast cancer.

   - ER+ disease must be documented by IHC per ASCO/CAP Guidelines[2].
   - HER2- disease must be documented by either IHC or in-situ hybridization per ASCO/CAP guidelines[3].

3. Participants who are resistant to standard therapy or for which no standard therapy is available or have received;

   - at least 2 prior endocrine regimens in any setting (neoadjuvant, adjuvant or advanced/metastatic). However, the number of prior cytotoxic chemotherapy regimen in the locally advanced or metastatic setting must be no more than 3 regimens.

   All such therapy must be discontinued at least 14 days prior to enrollment.

Informed Consent:

4. Capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Other Inclusion criteria:

5. ECOG PS 0 or 1 (Section 10.12).

6. Adequate Bone Marrow or Coagulation Function, defined as (with no transfusion of blood products or use of hematopoietic growth factors in the 28 days prior to enrollment):

   a. ANC $\geq$1,500/mm^3 or $\geq$1.5 x 10^9/L;

   b. Platelets $\geq$100,000/mm^3 or $\geq$100 x10^9/L;

   c. Hemoglobin $\geq$9 g/dL;

   d. aPTT $\leq$1.25$\times$ ULN and INR $\leq$1.25.

7. Adequate Renal Function, defined as an estimated creatinine clearance $\geq$60 mL/min as calculated using the method standard for the institution.

8. Adequate Liver Function, defined as:

   a. Total bilirubin $\leq$1.5 x ULN (<3 x ULN in a participant with documented Gilbert's syndrome);

b. AST and ALT ≤2.5 x ULN if there is NO liver metastasis; ≤5.0 x ULN if there is liver metastasis.

9. Participants with brain metastases must meet all the following conditions:

   a. Have completed their planned course of treatment;

   b. Have recovered from the acute effects of radiation therapy or surgery prior to first dose of drug;

   c. Have discontinued high dose corticosteroid treatment for these metastases for at least 4 weeks;

   d. Are neurologically stable as judged by the investigator;

   e. Participants who are diagnosed with a CNS metastasis during the screening period must also meet these criteria.

10. Resolution of acute effects of any prior therapy to either baseline severity or CTCAE version 5.0 Grade ≤1 (except for AEs not constituting a safety risk in the investigator's judgment).

11. Participants must agree and be capable of taking oral medication without crushing, dissolving, or chewing tablets.

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

Exclusion Criteria

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

Medical Conditions:

1. Participants with any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix, Bowen's disease.

2. Participants sustaining major surgery defined as a complex procedure performed under regional or general anesthesia with a recovery period of at least 4 weeks prior to study enrollment.

3. Known or suspected hypersensitivity or severe allergy to active ingredient/excipients of ARV-471.

4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study

participation or, in the investigator's judgment, make the participant inappropriate for the study.

5. Radiation therapy within 4 weeks of first dose of study drug or prior irradiation to >25% of the bone marrow (see Section 10.10 Bone Marrow Reserve in Adults). Palliative radiation for the alleviation of pain due to bone metastasis will be allowed during the study.

Prior/Concomitant Therapy:

6. Concurrent administration of medications, foods or herbal supplements that are strong inhibitors or inducers of CYP3A4 and drugs with a known risk of causing Torsade de Pointes or QT interval prolongation. Prior use of strong CYP3A inhibitors and drugs with a known risk of causing Torsade de Pointes or QT interval prolongation must be stopped 7 days before enrollment and strong CYP3A inducers must be stopped 14 days before enrollment. Refer to Sections 6.8 Concomitant Therapy and 10.8 (Appendix 8).

7. Prior treatment with ARV-471.

8. Systemic anticancer therapy chemotherapy or endocrine therapy within 14 days prior to study entry (6 weeks for mitomycin C or nitrosoureas). If the last immediate anticancer treatment contained an antibody-based agent(s) (approved or investigational), then an interval of 28 days or 5 half-lives (whichever is shorter) of the agent(s) prior to receiving the study intervention treatment is required.

9. Participants who have initiated therapy with bone-modifying agents (bisphosphonates, denosumab, or similar) within 14 days of enrollment (participants who are receiving bone-modifying agents are eligible for this study provided the bone-modifying agent was started more than 14 days prior to study enrollment).

10. Previous high-dose chemotherapy requiring stem cell rescue.

Prior/Concurrent Clinical Study Experience:

11. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry. A participant may be eligible even if they are in the follow-up phase of an investigational study as long as they haven't received treatment in the study for 5 half-lives of the agents.

Diagnostic Assessments:

12. Serum pregnancy test (for females of childbearing potential) positive at screening and/or a breastfeeding participant (including females who are currently breastfeeding or intend to temporarily interrupt breastfeeding).

13. Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) HBV, HCV, and known HIV or AIDS-related illness. Comments regarding specific circumstances follow.

    a. COVID-19/SARS-CoV-2: This protocol excludes participants with active infections, as noted above. While SARS-CoV-2 testing is not mandated for entry into this protocol, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, he/she is excluded.

    b. HIV: In equivocal cases, participants whose viral load is negative may be eligible. HIV seropositive participants who are otherwise healthy and at low risk for AIDS-related outcomes could be considered eligible. Potential eligibility for a specific HIV positive protocol candidate should be evaluated and discussed with the sponsor prior to any screening, based on current and past CD4 and Tcell counts, history (if any) of AIDS defining conditions (eg, opportunistic infections), and status of HIV treatment. Also, the potential for drug-drug interactions will be taken into consideration.

    c. HBV:

        - Participants with active, uncontrolled bacterial, fungal, or viral infection, including HBsAg positive.

        - Participants with positive HBsAb and positive HBcAb are allowed to participate in the study if they have negative HBV DNA test at screening but HB viral load should be monitored for re-activation every 12 weeks.

        - Participants with HBsAb positive who get vaccinated with HBV are exempted from the testing of HB viral load.

        - Participants who test positive for HBV viral load at any time during the study will interrupt administration of ARV-471, and should be considered for consultation with a hepatologist and initiation of antiviral therapies (eg, nucleoside antagonist) in accordance with the JSH Guidelines for the management of Hepatitis B Virus infection.

    d. HCV:

        - Positive HCV antibody is indicative of infection but may not necessarily render a potential candidate ineligible, *(https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf).*

14. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF>470 ms, complete LBBB, signs of an acute or indeterminate age myocardial

infarction, ST-T interval changes suggestive of active myocardial ischemia, second or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QTcF is >470 ms, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. QTcF exceeds 470 ms, or QRS complex exceeds 120 ms, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS complex values should be used to determine the participant's eligibility. Computer interpreted-ECGs should be over-read by a physician experienced in reading ECGs before excluding participants. Cases must be discussed in detail with the sponsor to judge eligibility.

15. Any of the following in the previous 12 months: myocardial infarction, long QT syndrome, Torsade de Pointes, clinically important atrial or ventricular arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), serious conduction system abnormalities (eg, bifascicular block [defined as right bundle branch and left anterior or posterior hemiblock], 3rd degree AV block), unstable angina, coronary/peripheral artery bypass graft, symptomatic CHF, New York Heart Association class III or IV, cerebrovascular accident, transient ischemic attack, symptomatic pulmonary embolism, and/or other clinical significant episode of thrombo-embolic disease. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade (Grade ≥2 in the case of asymptomatic lone atrial fibrillation). If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 ms, the participant may be considered eligible. Participants with cardiac rhythm device/pacemaker must be discussed in detail with the sponsor to judge eligibility.

16. History of symptomatic cardiac valve disease. Participants with mitral valve prolapse which is asymptomatic or not associated with clinically significant sequalae (eg, mitral regurgitation) are eligible. Any case of mitral valve prolapse must be discussed with the sponsor prior to enrollment to confirm eligibility.

17. Active inflammatory gastrointestinal disease, chronic diarrhoea, known diverticular disease or previous gastric resection or lap band surgery.

Other Exclusions:

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

Intervention Groups and Duration

ARV-471 will be administered orally QD with food, in continuous dosing over 28-day cycles. A participant may continue treatment at the discretion of the investigator until a treatment discontinuation criterion is met (see Section 7.1).

All treatment-related Grade 3 AEs should have their dose interrupted until return to Grade ≤1 or baseline. Study drug may be resumed using the modification guidelines in Table 6.

All treatment-related Grade 4 AEs should have their study treatment discontinued.

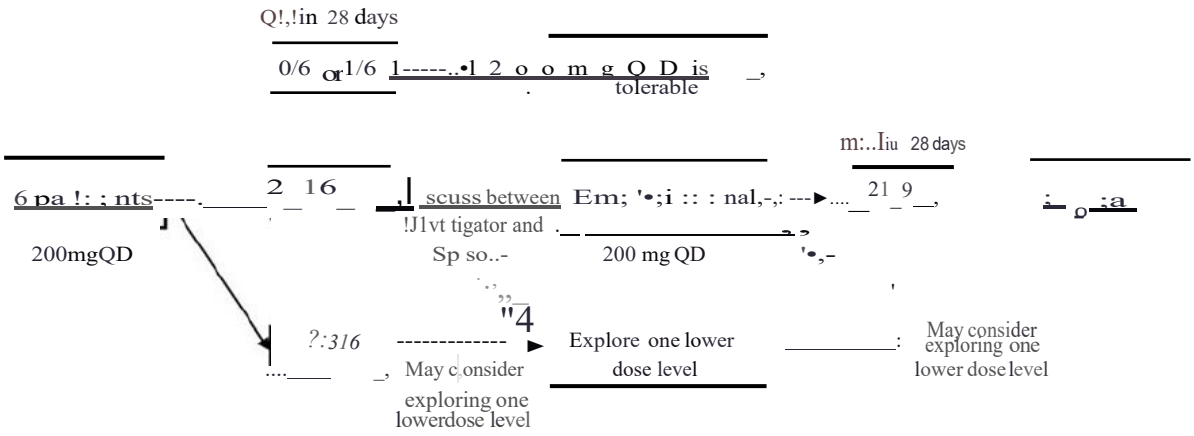
Following dosing intenuption or cycle delay due to toxicity, the study intervention dose may need to be reduced when ti·eatment is resumed. Dose reduction of study intervention by 1 dose level (see Table 5) will be allowed depending on the type and severity of toxicity encountered. Pa1ticipants requiring more than 1 dose reduction will be discontinued from the ti·eatment and entered into the Follow-up phase, unless othe1wise agreed between the investigator and the sponsor.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

The prima1y endpoint of this study is first cycle DLT. The occunence ofDLTs observed in the dosing coho1t in Japanese population is used to confnm the tolerability of the RP3D that was detennined in Study ARV-471-mBC-101 conducted outside Japan. The target DLT rate is 33%. If a propo1tion of observed DLTs in this study is less than 33%, the tolerability of the RP2D in Japanese population is considered to be confmned. AEs constituting DLTs will be listed. Confmnation of the tolerability of the RP2D will be perfo1med using the DLT evaluable set (see Section 9.2).

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each 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. Schedule of Activities

Visit Identifier Abbreviations used in this table may be found in Section 10.14 (Appendix 14).	**Screening (28 days prior C1D1)[1]**	**Study Treatment Period 1 Cycle = 28 days**								**EOT/Withdrawal[2]**	**Follow-up[3]**
		Cycle 1[4]						**Cycle 2 and beyond[4]**			
		Day 1	**Day 2**	**Day 8**	**Day 15**	**Day 16**	**Day 22**	**Day 1**	**Day 15**		
Visit Window		**NA**	**NA**	(±2)	(±2)	**NA**	(±2)	**Cycle 2:** (+2) **Cycle 3+:** (±2)	(±2)		
Informed consent[5]	X										
Medical history[6]	X										
Eligibility Criteria and Registration[7]	X										
Clinical Evaluation											
PE[8]	X									X	
Brief PE[8]		X		X			X	X	X		X
Height	X										
Weight	X	X						X		X	
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	
ECOGPS	X	X						X		X	X
Treatment											
ARV-471[10]		X	X	X	X	X	X	X	X		
Disease assessments											

Visit Identifier Abbreviations used in this table may be found in Section 10.14 (Appendix 14).	**Screening (28 days p1·ior C1D1)[1]**	**Study Treatment Period 1 Cycle = 28 days**								**EOT/Withdrawal[2]**	**Follow-up[3]**
		Cycle 1[4]						**Cycle 2 and bevond[4]**			
		Day 1	**Day 2**	**Day 8**	**Day 15**	**Day 16**	**Day 22**	**Day 1**	**Day 15**		
Visit Window		**NA**	**NA**	(±2)	(±2)	**NA**	(±2)	**Cycle 2:** (+2) **Cycle 3+: (±2)**	(±2)		
CT/MRI scans[11]	X	Every 8 weeks from ClDl, then every 12 weeks from C7Dl (±7 davs)								X	
Bone scan[12]	X										
Safety Assessments											
Serious and nonserious AE monitoring[13]	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatment(s) [14]	X	X	X	X	X	X	X	X	X	X	X
Hematology[15]	X	X		X	X		X	X	X	X	
Chemistry[16]	X	X		X	X		X	X	X	X	
Coagulation[17]	X	X						X		X	
Thyroid function[18]	X										
Viral disease assessment[19]	X										
Urinalvsis[20]	X	X								X	
Electrocardiogram	X	Refer to Table 2									
Echocardiogram[21]	X										
Pregnancy test[22] and contraception check[23]	X	X						X		X	X
PK assessments											
Blood sample for ARV-471	Refer to Table 2										
PD or phannacogenomic assessments											
Tumor biopsy (optional) [24]	X							X		X	
								■			

Footnotes for Schedule of Activities

1. Screening: To be completed within 28 days prior to start of study treatment.

2. EOT/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new antitumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).

3. Follow-up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, participants will return to undergo review of pregnancy test, contraception check, prior/concomitant medications, ECOG PS, brief PE, and assessment for AEs and SAEs. Participants continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

4. Day relative to start of ARV-471 (Day 1).

5. Informed consent must be obtained prior to any study specific procedures (see Section 10.1.3).

6. Medical history includes history of disease process other than the cancer under study (active or resolved) and concurrent illness, prior treatments and any current medical treatments for any condition.

7. Eligibility Criteria and Registration: Participant number assigned by the sponsor (see Section 5.1 and 5.2).

8. PE must be performed within 48 hours prior to a scheduled visit. A full PE is required at Screening and EOT/Withdrawal visits. There is no need to repeat PE if screening assessment is within 4 days of Cycle 1 Day 1. A brief PE should be performed at other visits as indicated. A brief PE will be symptom directed exam and assessment for emergent toxicities or changes from prior visits (see Section 8.2.1).

9. Vital Signs includes temperature, BP, respiratory rate and pulse rate. BP and pulse rate should be recorded in the sitting or semi-recumbent position after 5 minutes of rest (recommended same position should be used throughout the study). On in-clinic dosing days, vital signs should be measured prior to dosing (pre-dose) (see Section 8.2.2).

10. ARV-471 will be administered orally once daily with food during each 28-day cycle. On days of scheduled clinic visits, ARV-471 should be undertaken in the clinic (ie, not at home). Time of dose should be recorded in the source documents and eCRF. On Day 1, 2, 15 and 16, participants will be provided a light meal prior to their ARV-471 dose given in the clinic. On other clinic visit days participants will also take a light meal prior to their ARV-471 dose given in the clinic. Participants will self-dose as described above, except for doses that will be administered in the clinic (see Section 6.1.1).

11. CT/MRI scans will be performed within 28 days prior to Cycle 1 Day 1 and will include all known or suspected disease regions. Scans obtained as part of standard of care before consent was signed are acceptable if obtained within 28 days prior to Cycle 1 Day 1. Imaging will include chest, abdomen, and pelvis CT or MRI scans (same modality should be used throughout the study). If MRI is performed for the abdomen and pelvis examinations at baseline, then at least a non-contrast CT of the chest must be performed as well. CT or MRI scans to be done every 8 weeks (±7 days) from the date of first dose (Cycle 1 Day 1), for the first 24 weeks of study treatment, then every 12 weeks (±7 days) thereafter. Scans should be performed independent of dose

delays. Tumor assessments will continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST version 1.1, study drug discontinuation (for participants who discontinued treatment for reasons other than RECIST-defined disease progression), initiation of new anticancer therapy, or discontinuation of participant from overall study participation (eg, death, participant's request, lost to follow-up, study terminated by sponsor), whichever occurs first. Given the exploratory nature of the study, confirmation of response (CR or PR) is preferred (see Section 10.11). Tumor assessments should be repeated at the EOT/Withdrawal visit if more than 8 weeks or 12 weeks (as applicable) have passed since the last evaluation.

12. Bone scans must be performed in all participants at baseline within 28 days prior to Cycle 1 Day 1. Scans obtained as part of standard of care before consent was signed are acceptable if obtained within 28 days prior to Cycle 1 Day 1. Bone scans performed >28 to 45 days prior to enrollment as part of clinical care unrelated to this study may be acceptable pending discussion with the sponsor. For participants with bone lesions identified only by bone scan at baseline, additional studies (eg, X-ray, CT scan with bone windows or MRI) must be performed of these lesions at baseline and for follow-up assessments.

13. Serious and nonserious AE monitoring: From the time the participant provides informed consent through and including a minimum of 28 calendar days after the last study drug administration (active collection period). If the participant begins a new anticancer therapy, the period for recording non-serious AEs on the eCRF ends at the time the new treatment is started. However, any SAEs related to study treatment occurring during the active collection period must still be reported to the sponsor or designee and recorded in the eCRF, irrespective of any intervening treatment (see Section 8.3.1 and 8.3.3).

14. All concomitant medications, over-the-counter, and non-drug supportive interventions should be recorded in the eCRF including supportive care drugs; eg, anti-emetic treatment and prophylaxis, palliative radiotherapy on study is permitted (eg, skeletal administration for mBC), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions).

15. Hematology: There is no need to repeat on Cycle 1 Day 1 if screening assessment is performed within 3 days prior to that date. Assessments performed at each subsequent visit should be performed within 2 days prior to dosing. See Section 10.2 for more information.

16. Chemistry: There is no need to repeat on Cycle 1 Day 1 if screening assessment is performed within 7 days prior to that date. See Section 10.2 for more information.

17. Coagulation: There is no need to repeat on Cycle 1 Day 1 if screening assessment is performed within 3 days prior to that date. See Section 10.2 for details.

18. Thyroid function: ie, TSH.

19. Viral disease assessment: HBsAg, HBcAb, HBsAb, HCVAb, and HIV testing to be conducted by local laboratory when required by local regulations or if warranted by participant history.

20. Urinalysis: Local urine dipstick testing is acceptable. There is no need to repeat on Cycle 1 Day 1 if screening assessment is performed within 7 days prior to that date. See Section 10.2 for more information.

21. Repeat as clinically indicated (refer to Section 8.2.4).

22. Pregnancy test: A serum pregnancy test will be conducted on all women of childbearing potential at Screening. Urine pregnancy tests will be done on study. If a mine test cannot be confinned as negative (eg, an ambiguous result), a serum pregnancy test is required.

23. Contraception check: The investigator or qualified designee will discuss with the pa1ticipant the need to use **1** highly effective contraception method consistently and coITectly and document such conversation in the pa1ticipant's cha11. In addition, the investigator or qualified designee will instruct the participant to call illllllediately if one selected contraception method is discontinued, or if pregnancy is known or suspected of the participant or the participant's partner. Male pa1ticipants who are able to father children will need to affum that they meet the criteria for the coITect use of2 of the selected methods of contraception (see Section 10.4).

24. **Tumor biopsy: If a participant has a tumor accessible for biopsy at a site of disease, a biopsy will be done at Screening visit and at Cycle 2 Day 1 but no later than end of Cycle 2 visit. Screening and on-treatment biopsy is optional.** CCI [redacted] An EOT/Withdra:wal biopsy should only be perfo1med if a screening biopsy was perfo1med and an on-treatment biopsy was NOT performed at Cycle 2 Day **1** or before Cycle 2. This EQT/Withdrawal biopsy should be performed while the pa1ticipant is still on study drug.

25. CCI [redacted]

26. CCI [redacted]

Pharmacokinetic Sampling and ECG

Table 2. Schedule of PK and ECG Assessment

Visit Identifier	Study Treatment Pe1iod 1 Cvcle = 28 davs								EOT/Withdrnwal[1]
	Cycle 1						Cvcle 2 and 3		
	Dav 1	Day2	Day8	Dav15	Dav 16	Dav22	Dav 1	Dav 15	
Visit Window	**NA**	**NA**	(±2)	(±2)	**NA**	(±2)	**Cycle 2:** (+2) **Cycle 3:** (±2)	(±2)	
PK[2,3]									
Pre-dose (if dosing day)	X	X (24hours)	X	X	X (24 hours)	X	X	X	x5
1hour	X			X					
2hours	X			X					
4hours	X			X					
6hours	X			X					
8hours	X			X					
12 hours (optional)[4]	X			X					
Electrocardiogram[6]									
Pre-dose	X	X	X	X	X	X	X	X	x5
4hours (±25 min)	X			X					
6 or 8 homs (±45 min)	X			X					

Footnotes for Schedule of PK and ECG Assessment

1. EQT/Withdrawal: visit to be perfo1med as soon as possible but no later than 4 weeks from the last dose of study drng and prior to initiation of any new antitumor therapy.

2. On Days 1, 2, 15 and 16, the pa1ticipant will be provided a light meal after the pre-dose sample prior to their ARV-471 dose in the clinic. All pa1ticipants will be hospitalized for PK sampling and ECG assessment during Day 1 to 2 and Day 15 to 16 in the first cycle of dosing of ARV-471.

3. With regard to serial PK sampling on Cycle 1 Days 1 and 15, samples should be collected within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample). For pre-dose samples on Cycle 1 Days 2, 8, 16 and 22, Cycle 2 Days 1 and 15, and Cycle 3 Days 1 and 15, pre-dose samples collected within 24 hours± 10% (ie,2 hours and 24 minutes) after the dose administration on the day prior to the pre-dose PK sampling AND collected prior to administration of ARV-471 on that day (for pre-dose PK samples) will be considered protocol compliant (refer to Section 8.4).

4. Collection of PK sample at 12 hours is optional.

5. A single time point assessment can be collected if the participant does not receive study treatment on this visit.

6. Standard 12 Lead ECG: ECGs will be collected at times specified in the SoA. The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12 lead ECGs (triplicate) will be performed approximately 2 minutes apart to determine mean QTcF interval. All 12 lead ECGs should be confirmed by a qualified individual at the institution. When coinciding with blood sample draws for PK, ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (≥60 msec from the baseline and >500 msec), the ECGs should be re-evaluated by a qualified individual at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated (refer to Section 8.2.3).

2. INTRODUCTION

ARV-471, a PROteolysis-TArgeting Chimera (PROTAC®) hetero-bifunctional small molecule is currently being investigated in patients with ER+/HER2- locally advanced or mBC.

2.1. Study Rationale

The purpose of this study is to confirm safety and tolerability at the RP3D of ARV-471 in Japanese participants with ER+/HER2- locally advanced or mBC.

2.2. Background

2.2.1. Breast Cancer

In Japan, breast cancer is the fourth leading cause of cancer death in women, with approximately 15,500 people expected to die with breast cancer in 2020. It is estimated that approximately 92,300 women were newly diagnosed with breast cancer, which is the first incidence in all cancers in 2020[4]. Regarding men, it is estimated that approximately 700 people were newly diagnosed with breast cancer, which is <1% in all breast cancer in 2020[4].

Treatment options for advanced breast cancer or mBC depend on many different factors, including whether the tumors express ER and/or progesterone receptor or HER2. The standard of care for women with mBC is endocrine therapy, chemotherapy and/or targeted therapy alone or in combination. Patients with ER+/HER2- mBC are treated with endocrine therapy, sometimes in combination with targeted drugs such as CDKi. In patients with aggressive disease or whose disease continues to progress on endocrine therapy, chemotherapy may be prescribed.

The current standard of care for patients with ER+/HER2- mBC is endocrine therapy ± CDKi or mTOR inhibitor. Endocrine therapies include ovarian ablation or suppression (for premenopausal women), tamoxifen (a selective ER modulator, SERM), aromatase inhibitors, and fulvestrant (a selective ER downregulator, SERD). Metastatic BC remains incurable, and sequencing of endocrine therapies is the recommended approach for the treatment of ER+ breast cancer. The addition of targeted agents including CDKi and mTOR inhibitors to a backbone of endocrine therapy further improves patient outcomes.

Fulvestrant is considered a cornerstone component of ER-targeted endocrine regimens in the advanced disease setting, and works via an indirect mechanism of protein degradation, resulting in destabilization of ER. Single agent fulvestrant is dosed at 500 mg IM on Days 1, 15, and 29 and once monthly thereafter. Efficacy of fulvestrant was established by comparison to the selective aromatase inhibitor anastrozole in 2 randomized, controlled clinical trials in postmenopausal women with locally advanced or mBC[5]. All participants had progressed after previous therapy with an antiestrogen or progestin for breast cancer in the adjuvant or advanced disease setting. In both trials, eligible participants with measurable and/or evaluable disease were randomized to receive either fulvestrant 250 mg IM once a month (28 days + 3 days) or anastrozole 1 mg orally once a day. Results of the trials, after a minimum follow-up duration of 14.6 months, ruled out inferiority of fulvestrant to

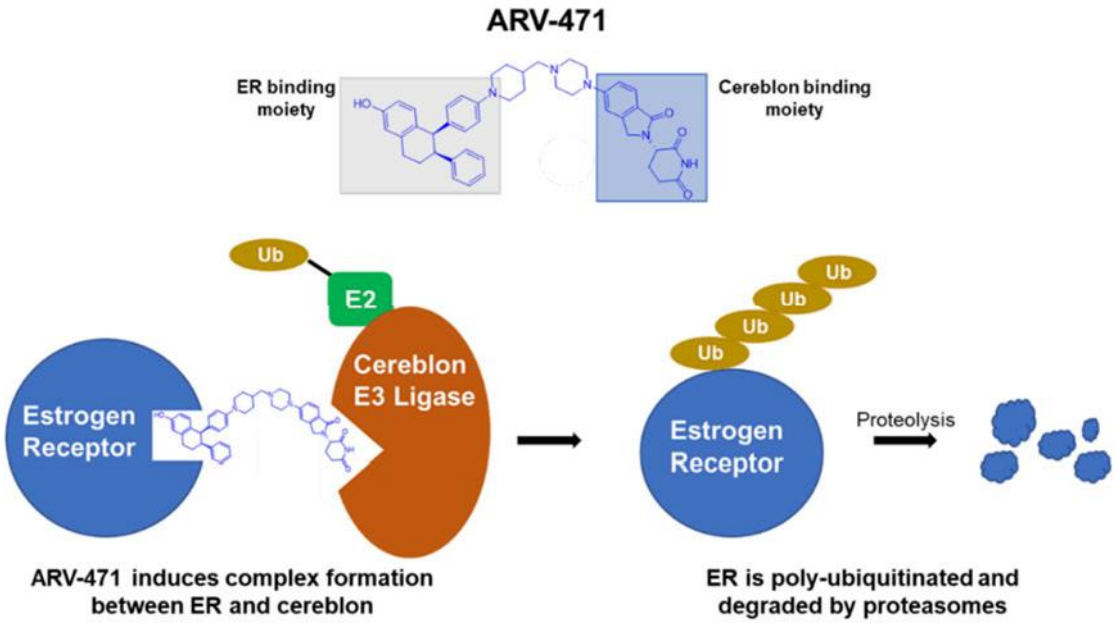
anastrozole. There was no statistically significant difference in OS between the 2 treatment groups after a follow-up duration of 2 years or more. A third study compared fulvestrant 500 mg dose to fulvestrant 250 mg dose. Results of this study after a minimum follow-up duration of 18 months showed that PFS was statistically significantly superior with fulvestrant 500 mg versus fulvestrant 250 mg (6.5 months versus 5.4 months, respectively). There was no statistically significant difference in OS between the 2 treatment groups (25.1 months for fulvestrant 500 mg and 22.8 months for fulvestrant 250 mg). ORR were similar; the RR for the 500 mg dose was 13.8 % (95% CI 9.7%-18.8%) and for the 250 mg dose was 14.6% (95% CI 10.5%-19.4%)[5].

2.2.2. PROTAC® and ARV-471

A new technology termed PROTAC, proteolysis targeting chimera, has been developed for inducing the protein degradation by a targeting molecule. This technology takes advantage of a moiety of targeted protein and a moiety of recognizing E3 ubiquitin ligase and produces a hybrid molecule to specifically knock down a targeted protein. PROTAC is composed of a short peptide that binds to E3 ubiquitin ligase and a small molecule that binds to target protein followed by polyubiquitination and proteasome degradation of target[6].

ARV-471 is a PROTAC small molecule that induces active degradation of ER. ARV-471 is being developed for the treatment of patients with ER+/HER2- locally advanced or mBC. ARV-471 works by recruiting an E3 ligase to ubiquitinate ER which results in its subsequent degradation through the proteasome, a large, multi-subunit protein complex that degrades ubiquitinated proteins into small peptides (Figure 1).

Figure 1. A Schematic Diagram of PROTAC (ARV-471)



Such "active" degradation results in improved knockdown of tumor ER relative to fulvestrant in xenograft mouse models and produces TGI in vivo both as a single agent and in

combination with palbociclib. Unlike fulvestrant, which is administered via IM injections, ARV-471 is orally administered. Further, in early preclinical studies, ARV-471 has demonstrated greater ER degradation compared to other oral SERDs in clinical development, such as AZD9496 and RAD1901[1].

2.2.3. Nonclinical overview of ARV-471

Please refer to ARV-471 IB Section 5 for nonclinical details.

2.2.4. Clinical Overview of ARV-471

Currently, ARV-471 is being evaluated in one Phase 1/2 study (Study ARV-471-mBC-101).

2.2.4.1. Study ARV-471-mBC-101

2.2.4.1.1. Study design

Study ARV-471-mBC-101 (ClinicalTrials.gov Identifier: NCT04072952) is a Phase 1/2 FIH, open-label, 2-part, sequential group, 3+3 dose escalation (Part A), and cohort expansion (Part B) of single agent ARV-471 and a Phase 1b investigation of ARV-471 in combination with palbociclib to evaluate the safety and tolerability of ARV-471 (Part C), either as a single agent or in combination with palbociclib, in participants with locally advanced or mBC. The study will also characterize the first dose and steady state PK profile, assess preliminary antitumor activity, PD effects on exploratory biomarkers, and the safety of ARV-471 at the RP2D. The study consists of 3 parts:

- Part A – Phase 1 Dose Escalation aims to enroll up to 75 participants to determine the MTD and/or RP2D of ARV-471 as monotherapy. ARV-471 will be administered orally QD or BID with food for 28-day cycles.

- Part B – Phase 2 Cohort Expansion aims to enroll approximately 60 participants. Two single agent RP2D and schedules of ARV-471 at 200 mg QD and 500 mg QD. Participants will receive ARV-471 orally at the RP2D with food for 28-day cycles.

- Part C – Phase 1b Combination ARV-471 + palbociclib aims to enroll up to approximately 55 participants to determine the safety and recommended dose of ARV-471 in combination with palbociclib. Part C will include 3 dose-escalation levels for ARV-471 in combination with palbociclib: 200 mg QD (Cohort C1), 400 mg QD (Cohort C2), and 500 mg QD (Cohort C3). The starting dose of palbociclib in the approved dose and regimen, 125 mg once daily for 21 days followed by 7 days off treatment to complete a 28-day cycle.

As of 06 June 2022, 78 participants have been treated across 7 dose level cohorts in Part A using a once daily administration schedule [N=3 at 30 mg; N=3 at 60 mg; N=9 at 100 mg; N=7 at 120 mg; N=7 at 180 mg; N=8 at 200 mg; N=15 at 360 mg; N=22 at 250 mg BID/500 mg QD; and N=4 at 700 mg QD]. The sponsor evaluated 2 potential RP2D candidates of 200 mg QD and 500 mg QD in Part B and 200 mg QD was selected as the RP3D of ARV-471 from Part B. As of 06 June 2022, an additional 71 participants have been

treated in the current 200 mg QD or 500 mg QD dose cohort in Part B and 27 participants have been treated in Part C.

2.2.4.1.2. Pharmacokinetics and Product Metabolism

Blood samples for PK evaluation were collected from mBC participants receiving ARV-471. A chiral bioanalytical LC-MS/MS method was used for analysis of ARV-471 and ARV-473 for Parts A, B and C of Study ARV-471-mBC-101. ARV-473 is an epimer of ARV-471 with ER antagonistic but no degradation activity, and was formed to a limited extent in animals and humans although it is not thought to be formed via enzymatic conversion. PK parameter values for ARV-471 + ARV-473 are also reported. PK analyses were performed using noncompartmental analysis methods for Parts A and C. Preliminary PK data from Part A of Study ARV-471-mBC-101 were available from dose levels ranging from 30 mg to 700 mg administered either as QD or BID. Preliminary results indicated dose-dependent increases in C_{max} and AUC_{tau} for ARV-471, ARV-473, and ARV-471 + ARV-473 up to 500 mg total daily dose administered either as 250 mg BID or 500 mg QD on both Day 1 and Day 15 (see Table 3). The median T_{max} ranged from 4 to 7 hours across the dose levels. Geometric mean ARV-471 AUC_{tau} is 7324 ng•h/mL on Day 15 at 60 mg QD (N=3) and has exceeded the nonclinical efficacious range associated with TGI (AUC_{inf} = 5717 ± 2353 ng•h/mL, single 30 mg/kg in mice). Following 200 mg QD dosing (N=8), a geometric mean R_{ac} based on AUC_{tau} of 1.7 was observed between Day 1 and Day 15. The mean effective $t_{1/2}$ at steady state ($t_{½eff}$) ranged from 23 to 33 hours. The ratio of ARV-473/ARV-471, based on AUC_{tau}, on Cycle 1 Day 15 is 32%. These preliminary findings are similar to those observed exposures of ARV-473 relative to ARV-471 (≥26%) in toxicology studies in dogs and rats.

Table 3. Preliminary PK Data of ARV-471-mBC-101 Part A (Data Snapshot of 06 Jun 2022)

Dose	ARV-471 Geometric Mean (GCV%)						ARV-473 Geometric Mean (GCV%)						ARV-471 + ARV-473 Geometric Mean (GCV%)					
	Day 1 (Single Dose)			Day 15 (Multiple Dose)			Day 1 (Single Dose)			Day 15 (Multiple Dose)			Day 1 (Single Dose)			Day 15 (Multiple Dose)		
	N	AUC_{tau} (ng•h/m)	C_{max} (ng/m)	N	AUC_{tau} (ng•h/m)	C_{max} (ng/m)	N	AUC_{tau} (ng•h/m)	C_{max} (ng/m)	N	AUC_{tau} (ng•h/m)	C_{max} (ng/m)	N	AUC_{tau} (ng•h/m)	C_{max} (ng/m)	N	AUC_{tau} (ng•h/m)	C_{max} (ng/m)
30 mg QD	3	1713 (7%)	109 (6%)	3	4051 (26%)	219 (27%)	3	193 (4%)	8 (4%)	3	1279 (33%)	58 (32%)	3	1907 (6%)	116 (5%)	3	5334 (27%)	276 (28%)
60 mg QD	3	2964 (33%)	194 (33%)	3	7324 (15%)	405 (8%)	3	323 (36%)	13 (38%)	3	2243 (8%)	108 (6%)	3	3287 (34%)	206 (33%)	3	9570 (14%)	500 (6%)
100 mg QD	8	4146 (57%)[c]	221 (87%)	7	8898 (39)	522 (46%)	8	443 (61%)[c]	17 (111%)	7	2515 (40%)	125 (46%)	8	4590 (57%)[c]	236 (88%)	7	11431 (39%)	648 (45%)
120 mg QD	7	6326 (21%)	404 (21%)	7	13714 (13%)	799 (6%)	7	674 (20%)	29 (25%)	7	3974 (24%)	191 (19%)	7	7005 (21%)	430 (21%)	7	17727 (15%)	991 (6%)
180 mg QD	7	9389 (16%)	555 (15%)	6	19225 (32%)	1062 (27%)	7	1014 (11%)	40 (24%)	6	5799 (34%)	273 (32%)	7	10408 (15%)	593 (14%)	6	25059 (32%)	1334 (27%)
200 mg QD	8	9114 (48%)	534 (52%)	8	15459 (34%)	866 (40%)	8	959 (43%)	40 (41%)	8	4990 (35%)	234 (34%)	8	10084 (47%)	569 (52%)	8	20480 (34%)	1091 (38%)
360 mg QD	15	12172 (32%)	748 (34%)	15	25931 (27%)	1502 (27%)	15	1352 (37%)	60 (34%)	15	8077 (34%)	382 (31%)	15	13540 (32%)	799 (34%)	15	34074 (28%)	1875 (26%)
500 mg QD	12	16765 (30%)[d]	1046 (31%)	11	34585 (35%)	1883 (31%)	12	1797 (28%)[d]	80 (26%)	11	10198 (41%)	480 (42%)	12	18567 (30%)[d]	1116 (31%)	11	44908 (36%)	2360 (32%)
700 mg QD	1	19639[e]	1450[e]	1	26572[e]	1530[e]	1	2009[e]	92[e]	1	7387[e]	325[e]	1	21649[e]	1532[e]	1	33960[e]	1845[e]
250 mg BID (500 mg total daily dose)	10	2924 (32%)[a]	663 (18%)	8	20559 (34%)[b]	2058 (34%)	10	179 (48%)[a]	52 (26%)	8	7393 (52%)[b]	695 (55%)	10	3106 (33%)[a]	709 (18%)	8	28120 (38%)[b]	2733 (39%)
400 mg AM/300 mg PM (700 mg total daily dose)	3	3798 (102%)[a]	716 (131%)	2	35360, 14815[b,e]	3360, 1510[e]	3	220 (96%)[a]	47 (119%)	2	12334, 3790[b,e]	1060, 378[e]	3	4018 (101%)[a]	757 (130%)	2	47694, 18605[b,e]	4360, 1888[e]

AUC_{0-8}= area under the plasma concentration-time curve from zero to 8 hours; AUC_{0-12}=area under the plasma concentration-time curve from 0 to 12 hours; AUC_{tau}=area under the plasma concentration-time curve over the dosing interval, where tau = 24 hours for once daily dosing and 12 hours for twice daily dosing; BID=twice daily; C_{max}=maximum plasma concentration; GCV=geometric coefficient of variation; QD=once daily.

a AUC_{0-8}
b AUC_{0-12}
c N=7
d N=11
e Expressed as individual values when N<3.

PK data as of 6 Jun 2022 analyzed at ICONplc.com/PRA.

2.2.4.1.3. Safety

As of 06 June 2022, a total of 176 participants have received at least 1 dose of ARV-471 in Parts A, B and C.

Regardless of study drug attribution and grade, TEAEs were observed in 157 of the total 176 participants treated with ARV-471 in the ongoing trial (all parts). Please refer to ARV-471 IB Section 6.5 for details.

2.2.4.1.3.1. Part A – Dose Escalation (n=78)

The most common TEAEs (regardless of attribution to study drug) observed in ≥10% of participants, listed in decreasing order of frequency, were: fatigue (33.3%), nausea (33.3%), constipation (30.8%), arthralgia (17.9%), vomiting (17.9%), back pain (16.7%), diarrhoea (16.7%), headache (16.7%), decreased appetite (15.4%), AST increase (14.1%), hot flush (14.1%), hyperglycaemia (12.8%), pain in extremity (12.8%), insomnia (11.5%), ALT increased (10.3%), and dizziness (10.3%).

A total of 13 participants (16.7%) experienced TEAEs of Grade ≥3 severity. The Grade 3 TEAEs that occured in 1 participant each were nausea, stomatitis, arthralgia, fatigue, AST increased, electrocardiogram QT prolonged, amylase increased, blood alkaline phosphatase increased, lipase increased, headache, presyncope, embolism, venous embolism, procedural pain, humerus fracture, acute kidney injury, and malignant pleural effusion. Grade 3 hypertension occurred in 2 participants. The Grade 4 TEAEs of hypoglycaemia, neutrophil count decreased, and neutropenia occurred in 1 participant each. The Grade 5 TEAE of cardiac arrest occurred in 1 participant and was unrelated to ARV-471.

A total of 54 of 78 participants (69.2%) had at least 1 TEAE considered potentially related to ARV-471. The most commonly reported TRAEs observed in ≥10%, listed in decreasing order of frequency were nausea (25.6%), fatigue (21.8%), constipation (12.8%), arthralgia (10.3%), decreased appetite (10.3%), hot flush (10.3%), and vomiting (10.3%). Four participants (5.1%) experienced 6 Grade 3 TRAEs: headache lasting 1 day, asymptomatic amylase increased and lipase increased, nausea and asymptomatic electrocardiogram QT prolonged, and venous embolism that occurred after a minor procedure (bone biopsy). There were no Grade 4 or Grade 5 TRAEs reported.

2.2.4.1.3.2. Part B – Dose Expansion (n=71)

A total of 62 of the 71 participants (87.3%) reported at least 1 TEAE, and the most commonly reported TEAEs observed in ≥10% of participants, listed in decreasing order of frequency, include fatigue (39.4%), nausea (21.1%), constipation (16.9%), arthralgia (16.9%), AST increased (12.7%), decreased appetite (11.3%), headache (11.3%), and back pain (11.3%).

A total of 16 participants (22.5%) experienced a total of 23 TEAEs of Grade ≥3 severity. The Grade 3 TEAEs that occurred in 1 participant each were intestinal obstruction, muscular weakness, AST increased, ALT increased, blood alkaline phosphatase increased, electrocardiogram QT prolonged, brain oedema, seizure, syncope, thrombocytopenia,

cholangitis, neutropenia, spinal cord compression, upper gastrointestinal haemorrhage, fatigue, pyrexia, back pain, and decreased appetite. The Grade 3 TEAE of anaemia was reported in 2 participants. The Grade 4 TEAEs of hyperbilirubinaemia, hypercalcaemia and hepatic haemorrhage were reported in 1 participant each. A Grade 5 TEAE of acute respiratory failure was reported in 1 patient, after that participant presented with progressive malignant pleural effusion.

A total of 51 participants (71.8%) experienced at least 1 TRAE, and the most commonly reported TRAEs observed in ≥10% of participants were fatigue (33.8%), nausea (16.9%), and arthralgia (12.7%). Five participants (7.0%) experienced 6 TRAEs, with severity of Grade ≥3, including Grade 3 events of electrocardiogram QT prolonged, thrombocytopenia, neutropenia, decreased appetite, and fatigue. There was 1 Grade 4 TRAE of hyperbilirubinaemia. There were no Grade 5 TRAEs reported.

2.2.4.1.3.3. Part C – Phase 1b Dose Escalation of Combination of ARV-471 + palbociclib (n=27)

A total of 24 of 27 participants (88.9%) reported at least 1 TEAE. The most common TEAEs observed in ≥20% of participants, include neutrophil count decreased (51.9%), fatigue (44.4%), neutropenia (37.0%), platelet count decreased (33.3%), anaemia (29.6%), nausea (25.9%), cough (22.2%), diarrhoea (22.2%), and white blood cell decreased (22.2%).

2.2.5. Rationale of dose selection in Phase 1 study in Japan

Two single agent RP2D of ARV-471 at 200 mg QD and 500 mg QD were selected from Part A and 200 mg QD was selected as the RP3D of ARV-471 from Part B in the FIH study (Study ARV-471-mBC-101) conducted outside Japan (see detail in Section 4.3). The RP3D, 200 mg QD will be investigated in the Phase 1 study in Japanese participants. No DLTs had been reported across 30 mg to 700 mg total daily doses in Study ARV-471-mBC-101. It is considered adequate to evaluate safety and tolerability at the RP3D, 200 mg QD in Phase 1 study in Japanese participants. If DLT is observed in ≥33% of participants at 200 mg QD, the investigation at the next lower dose level may be explored.

2.3. Benefit/Risk Assessment

ARV-471 may potentially benefit patients with locally advanced or mBC whose disease has progressed on currently approved standard of care agents. Preclinical and clinical data demonstrate that ARV-471 is a potent, selective, orally bioavailable degrader of ER, effectively lowers ER levels in tumors, and therefore it is anticipated to provide improved efficacy when compared to standard-of-care agent, fulvestrant.

Preclinical toxicology studies performed in rats and dogs with ARV-471 using QD oral administration showed it was well tolerated in both 7- and 28-day studies. The NOAELs for daily oral administration of ARV-471 to rats and dogs for 28 days were the highest dose of 100 mg/kg/day and 90 mg/kg/day, respectively. Based on the studies, potential adverse effects may include changes consistent with the pharmacologic activity of ARV-471 as an ER degrader, and similar to effects observed with other agents that target ER (eg, fulvestrant) when administered in healthy animals. These included reversible changes in the female

reproductive tissues such as increased ovaiy weight and occunence of ovai·ian cysts and corpus hemonhagicum, and uterine and cervical atrophy. Findings in the testis, epididymis, and prostate of male animals were consistent with effects seen in male animals dosed with ER inhibitors for at least 1 month and also showed si s of reversibili . An additional finding consisted of CCI [redacted] unaccompanied by changes to the CCI or to other CCI . The CCI findings seen in [redacted] (1) had no observed i act on the clinic s s of the anir not accompanied by any other changes in and and-- (2) were observed in only- at and were also observed in control animals; and (3) did not increase m frequency or severity with increasing dose or exposure level or duration of dosing. Overall, it is not expected that the fmdings listed above should impact clinical studies with ARV-471 for the treatment of ER+/HER2- paiticipants with locally advanced or mBC.

As of 06 June 2022, 78 pa1ticipants have been treated in Part A in Study ARV-471-mBC-101. No DLTs have been reported and MID has not been reached with ARV-471 monotherapy across total daily doses of 30 mg to 700 mg. The majority ofTRAEs ai·e Grade 1 or 2 in severity. The participant with Grade 3 venous embolism was the only patient who discontinued ARV-471 due to a TRAE. In addition, evidence of clinical benefit has been observed in this heavily treated population, with a 36.2% CBR among 25 of 69 evaluable paiticipants and a 8.6% ORR with 5 of 58 response-evaluable paiiicipants having confinned PRs.

QT Prolongation:

In the subsequent 3-month toxicity study in dogs, ARV-471 when administered at 90 mg/kg/day resulted in an approximate 13 msec prolongation of QT/QTc intervals on study Day 85 (nonadverse) associated with comparative exposure mai·gins to the 200 mg clinical dose of approximately 5.8x and 5.9x for AUC and Cmax, respectively. Both single- and repeat-dose studies up to Day 28 were negative for this effect at higher or equivalent dose/exposures, respectively. Neither ARV-471 nor ARV-473 inhibit the hERG channel in vitro at concentrations greater than 100 times those of clinical relevance. Overall, a potential concentration and time dependent impact on QT interval in the dog was observed.

Concentration-QTc modeling analysis of clinical data revealed a concentration-dependent increase in QTcF. Based on the model, a QTcF change from baseline is predicted to be 6.8 msec (90% CI: 5.7, 7.9) at the geometric mean Cmax for the sum of ARV-471 and ARV-473 (1,091 ng/mL) at steady-state after 200 mg QD dosing, while a QTcF change is predicted to be 14.7 msec (90% CI: 12.3, 17.1) at the geometric mean Cmax (2,360 ng/mL) after 500 mg QD dosing.

From the ongoing ARV-471-mBC-101 study, as of 06 Jun 2022, 13 paiticipants repo1ied TEAEs of electrocardiogram QT prolonged (12 pa1iicipants had TRAEs and in 1 paiiicipant the AE was considered as not related to ARV-471 per investigator).

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 >500 msec (1 of each at 180 mg, 200 mg, and 500 mg daily dose) and 4 participants had QTcF change from baseline >60 msec (1 at 200 mg, 2 at 500 mg and 1 at 700 mg daily dose).

No Grade 4/5 QT prolonged events have been reported of the 13 reported prolonged QTc events.

The Sponsor had an external cardiology expert evaluate the records of the participants with ECG abnormalities. The review concluded that of the 13 participants who reported QTc prolonged events, only 2 participants had a true diagnosis of QTc prolongation, of which low potassium and concomitant medications were confounding factors. The cardiologist concluded that due to the relatively low incidence of true treatment emergent ECG QTc abnormalities in the ARV-471-mBC-101 study, which had alternative explanations, ARV-471 does not adversely affect the ECG.

All events will continue to be monitored and participants will be excluded from ARV-471 trials if taking medications that are either known to prolong the QT interval or are associated with a risk of Torsades de Pointes, within 7 days prior to first study dose in all studies (until analyses of data from future studies are available). Concomitant use of such medications with ARV-471 will also be prohibited unless utilized with caution to treat a drug-related AE when no alternative is available. Protocols will include a list of drugs (adapted from https://crediblemeds.org/) that are associated with known QT risk.

TEAE of electrocardiogram QT prolonged has been identified to be of potential risk based on nonclinical findings, concentration-QTc modeling demonstrating concentration-dependent increases in QTcF, and from clinical data from Study ARV-471-mBC-101 Parts A, B and C.

Additional potential adverse effects of ARV-471 may be similar to those observed with ER-degrading agents such as fulvestrant, and include nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. The most common laboratory abnormalities with fulvestrant were increased hepatic enzymes (ALT, AST, and ALP[5]. Participants will be monitored closely throughout study participation. The sponsor will immediately notify the investigator of any additional safety or toxicology information which becomes available during the study.

More detailed information about ARV-471 is provided in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) ARV-471		
QT prolongation	Potential risk based on nonclinical findings. Concentration-QTc modeling analysis revealed a concentration-dependent increase in QTcF in a dose range of 30 mg to 700 mg total daily dose. Thirteen participants were reported with non-serious AE of QT interval prolongation in the ongoing FIH study (ARV-471-mBC-101); for 12 participants the event was considered related as per investigators. Per an external cardiology consultant review, only 2 participants had a true diagnosis of QTc prolongation, of which low potassium and concomitant medications were confounding factors. Clinical safety not yet fully characterized.	Participants will be monitored for QT interval changes with ECG monitoring at screening and during the study. Participants at high risk of QT prolongation as per Exclusion criteria #14 and 15 are excluded from participation in the study (see Section 5.2). Concomitant drugs predisposing to Torsade de Pointes or QT prolongation are prohibited as per Section 10.8. Study intervention will be temporarily interrupted, reduced, or permanently discontinued based on severity of the events occurred (see Section 6.5.1).
Venous embolism (VE)	Potential risk based on metastatic cancer setting and known class effect with ET (SERM, SERD, AI). One Grade 3 related serious VE case, with confounding factors of obesity, diabetes and immobility due to recent biopsy procedure, and a Grade 3 serious embolism case assessed as unlikely related to ARV-471 by the investigator, were reported in the Study ARV-471-mBC-101.	Participants with a history of clinically significant thromboembolic or cerebrovascular events are excluded from participation in the study as per Exclusion criteria #15 (see Section 5.2). Coagulation tests will be performed at screening and will be repeated on treatment. Suspicious of VE should be investigated, per local standard practice (eg, D-Dimer, fibrinogen, imaging). Study intervention will be temporarily interrupted, reduced, or permanently discontinued based on severity of the events occurred (see Section 6.5.1).
DDI	The potential for DDIs exists with ARV-471. In vitro assessment indicates CYP3A4 as the principal isoform responsible for CYP-mediated metabolism of ARV-471. Drugs that are inhibitors of CYP3A4 may increase the exposure	Medications known to strongly induce or inhibit CYP3A4, or act as a sensitive P-gp substrate are prohibited (see Section 10.8). The concomitant use of PPIs with ARV-471 is not recommended. If PPI treatment is required, ARV-471

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	of ARV-471, whereas drugs that are inducers of CYP3A4 may reduce the exposure of ARV-471. ARV-471 is also an in vitro inhibitor of P-gp and in vitro weak inhibitor of BCRP. BCRP substrates, rosuvastatin and sulfasalazine, may be used because safety risk is low. Studies conducted in fasted dogs and rats showed a pH effect on absorption when administered with famotidine (lowered PK at neutral pH). Elevated gastric pH may reduce ARV-471 absorption.	intake with a moderate-fat meal (400-800 calories, approximately 35% fat) is recommended. H_2 receptor antagonists or local antacids may be used, but should be staggered. Administer ARV-471 ≥2 hours before or after antacids. Administer ARV-471 ≥2 hours before or 10-12 hours after H_2 receptor antagonists (see Section 6.8).
Study Procedures		
CT or MRI procedures for tumor assessments	CT scans expose the participant to a small dose of radiation. The contrast dye used with the CT scan may cause pain or burning when injected. The dye may worsen kidney function for those with kidney disease or are dehydrated. The dye may cause an allergic reaction. MRI risks include possible reactions to metals due to magnets, loud noises from the machine causing hearing issues, increase in body temperature during long MRIs, and claustrophobia.	Only experienced professionals will conduct the CT or MRI procedures. The participant will be asked about allergies to the contrast dye. Medical history will be reviewed for kidney disease, and information will be provided to minimize dehydration. If possible, an open MRI can be used for those experiencing claustrophobia. The participant may be offered earplugs and/or headphones to minimize the noise.
Blood draws for PK, biomarker, blood chemistry, hematology, coagulation evaluations and CCI	The risks associated with blood collection commonly include discomfort, pain, redness and swelling and/or bruising where the blood is taken from the participant's arm. Sometimes bleeding can occur at the place where blood is drawn. Fainting and infection are rare occurrences associated with blood collection.	Only experienced professionals will conduct the blood draws.
Pre- and post-treatment tumor biopsies (optional)	The risks associated with biopsies include pain or discomfort during the biopsy, including slight, stinging pain when a local anesthetic is injected by needle to numb the area, pressure and dull pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness at the biopsy site. Other risks can include bleeding, swelling, scarring, bruising, nerve	To reduce these risks, the site of the biopsy will be anesthetized and sterile techniques will be used.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	damage and infection, which can be life threatening or fatal in rare cases.	
Other		
The COVID-19 pandemic may pose risks to study participation	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Use of telehealth, home health, etc will be utilized in the study to minimize potential exposure of trial participants to SARS-CoV-2 (see Section 10.9).

2.3.2. Benefit Assessment

In general, nonclinical toxicity studies have shown that ARV-471 is safe and well tolerated. And in initial data from participants with ARV-471 across multiple doses in FIH monotherapy study (n=78), most TRAEs were low grade, and no clear dose-dependent AEs were identified.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken 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 to participants with ER+/HER2- locally advanced or mBC.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To evaluate the safety and tolerability of ARV-471 at the RP3D	First cycle DLTs	The primary estimand for incidence of DLTs is DLT rate estimated based on data from DLT-evaluable participants during the DLT-evaluation period which is the first cycle of treatment (ie, 28 days) after the first dose of study intervention.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the overall safety profile	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing	NA
• To characterize the single-dose and multiple-dose PK of ARV-471 and ARV-473 (an epimer of ARV-471)	The following PK parameters will be assessed when applicable after a single dose and after multiple doses: single dose: AUC_{tau}, AUC_{last}, C_{max}, T_{max}, $t_{½}$, MRC_{max}, and $MRAUC_{tau}$ multiple doses; AUC_{tau}, AUC_{last}, C_{max}, C_{min}, C_{trough}, CL/F*, T_{max}, V_z/F*, R_{ac}, $t_{½}$, $t_{½eff}$, MRC_{max}, and $MRAUC_{tau}$ * ARV-471 only V_z/F and $t_{½}$ for single dose and multiple doses will be calculated only if data permit.	NA

Objectives	Endpoints	Estimands
• To explore preliminary antitumor activity [redacted]	Antitumor activity of ARV-471 will be assessed by evaluating the following: • ORR per RECIST version 1.1 • CBR based on the sUllllllation of CRs, PRs and SD of 24 weeks duration or longer • Time to event endpoints: PFS, DOR	NA
		[redacted]
[redacted] CCI	[redacted]	[redacted]
[redacted] CCI	[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This study is a single-countiy, non-randomized, open-label, Phase 1 study. This study will evaluate the safety, tolerability, PK, and preliminary efficacy of ARV-471 as monotherapy in Japanese paiiicipants with ER+/HER2- locally advanced or mBC.

One dose level of ARV-471, 200 mg QD which has been detennined as the RP3D as monotherapy in the FIH study (Study ARV-471-mBC-101) conducted outside Japan will be investigated. Six paiiicipants will receive ARV-471 at 200 mg QD. If none or 1 participant experience DLT dming the first cycle (1 Cycle= 28 days), ARV-471, 200 mg QD will be considered tolerable as monotherapy in Japanese pa1iicipants. lf2 pa1iicipants experience DLT, the investigator and the sponsor should discuss the safety and tolerability based on the available data, and then under the agreement between the investigator and the sponsor, an additional 3 paiiicipants at the same dose level, up to a total of 9 participants, will be enrolled to fmiher investigate the safety and tolerability of ARV-471 as monotherapy in Japanese paiiicipants. If no DLT is repo1ied in an additional 3 pa1iicipants, 200 mg QD will be considered tolerable in Japanese paiiicipants. IfDLT is observed in 33% of pa1iicipants at 200 mg QD, the investigation at the next lower dose level may be explored.

Paiiicipants who are inadequate to evaluate DLT (incomplete Cycle 1; fail to complete at least 75% of study drng ti·eatment in Cycle 1 for reasons other than DLT) must be replaced to adequately assess the safety of ARV-471.

Note: "Enrolled" means a pa1iicipant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the info1med consent process and assignment to study intervention. A paiiicipant will be considered enrolled if the info1med consent is not withdrawn prior to paiiicipating in any study activity. Potential participants who ai·e screened for the pmpose of detennining eligibility for the study, but do not paiiicipate in the study, are not considered enrolled.

In order to ensure paiiicipant safety, an interval of at least 1 day shall separate ti·eatment initiation for the first paiticipant and ti·eatment initiation for the second paiiicipant.

A paiiicipant may continue ti·eatment at the discretion of the investigator until a ti·eatment discontinuation criterion is met (see Section 7.1).

Paiiicipants who have evidence of radiographic disease progression may be considered for continued study therapy provided the investigator has detennined that they are still benefiting from study therapy; this must be reviewed and approved by the sponsor.

CCI [redacted]

4.2. Scientific Rationale for Study Design

The pmpose of this Phase 1 study is to evaluate the safety, tolerability, PK, and prelimina1y efficacy of ARV-471 as monotherapy in Japanese pa1iicipants with ER+/HER2- locally advanced or mBC. A target toxicity rate defined by DLT of <33% has u-aditionally been considered acceptable in the oncology field. The study with enrolhnent of 6 paiiicipants will allow for a reasonable number of treated paiiicipants to assess the safety, tolerability and PK of ARV-471 in Japanese paiiicipants.

CCI [redacted]

4.2.1. Choice of Contraception/Barrier Requirements

ARV-471 is known to cause risk for severe manifestations of developmental toxicity in humans or suspected on the basis of the intended pharmacology. Therefore, the use of a highly effective method of contraception is required (see Section 10.4).

ARV-471 is not genotoxic. However, nonclinical studies suggest risk for severe manifestations of developmental toxicity at relevant clinical exposures for ARV-471. Therefore, the use of a highly effective method of contraception is required (see Section 10.4).

Studies to evaluate the development toxicity of ARV-471 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Section 10.4).

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

Two single agent RP2D of ARV-471 at 200 mg QD and 500 mg QD were selected from Part A and 200 mg QD was selected as the RP3D of ARV-471 from Part B in the FIH study (Study ARV-471-mBC-101) conducted outside Japan. The RP3D, 200 mg QD, will be investigated in this study.

As of 06 June 2022, 176 participants have been treated in Study ARV-471-mBC-101 (Part A, n=78; Part B; n=71, Part C, n=27). ARV-471 has been well tolerated across total daily doses of 30 mg to 700 mg, without any DLTs observed. Most TRAEs were Grades 1 or 2. The MTD has not been reached, and the maximum administered dose was 700 mg total daily dose (administered 400 mg/300 mg BID) in Part A.

Two single agent ARV-471 doses at 200 mg QD and 500 mg QD were selected as the RP2D based on a review of PK, PD, safety and efficacy data from Part A in Study ARV-471-mBC-101. Two RP2Ds are being investigated in Part B in Study ARV-471-mBC-101 to further assess the activity of ARV-471.

The rationale for the selection of 2 RP2Ds is as follows:

<u>200 mg QD</u>

The 200 mg QD dose was selected as the RP2D based on a review of data from Part A in Study ARV-471-mBC-101 available as of 10 Feb 2021. At that time, a total of 38 participants had been treated with ARV-471 as monotherapy in Part A of the study. Doses received had been: 30 mg QD, n=3; 60 mg QD, n=3; 120 mg QD, n=7; 180 mg QD, n=7, 360 mg QD, n=14; and 250 mg BID, n=4. ARV-471 had been well tolerated at all doses tested, and reported safety data were as follows:

- No DLT or treatment-related SAEs had occurred at doses up to and including 180 mg QD.

- One treatment-related SAE occurred at the 360 mg QD dose level, a Grade 3 thromboembolic event. No DLT, additional treatment-related SAE or Grade 3/4 treatment-related events had been reported among the 13 participants who had completed at least 1 cycle of ARV-471 at 360 mg QD.

- The majority of reported AEs had been Grade 1. Grade 2 TRAEs had been reported at doses of 120 mg and higher. The only Grade 2 TRAE to occur in more than 1 participant was nausea (n=2).

- Preliminary PK, PD and efficacy data from the first 20 participants treated at doses up to 360 mg QD were as follows:

    - ARV-471 demonstrates dose-related PK, with doses of 60 mg QD and above resulting in exposures that far exceed the efficacious threshold for tumor regression in preclinical models.

    - Based on data from the first 3 dose levels (30 mg-120 mg), significant ER degradation (up to 90% with an average of 62%) was observed in participant tumor biopsies, which exceeds the 40%-50% degradation reported for fulvestrant. Degradation of both wild-type ER and ESR1-mutant proteins was observed[7,8].

    - A confirmed PR (with 51% shrinkage in tumor burden) was observed in a participant who received ARV-471 at 120 mg QD, and who was heavily pretreated with multiple lines of endocrine therapy and prior CDK4/6.

    - Shrinkage of measurable lesions was observed in 71% (10/14) of evaluable participants, and occurred across multiple dose levels.

    - The CBR (defined as SD persisting ≥24 weeks, or a best response of confirmed CR or PR) was 42% (5/12) among evaluable participants up to 180 mg, which exceeds the CBR (<20%) reported for fulvestrant in a similar population. Clinical benefit was also observed across dose levels.

<u>500 mg QD</u>

As of 13 April 2021, the dose escalation has proceeded through 30 mg QD, 60 mg QD, 120 mg QD, 180 mg QD, 360 mg QD, and 500 mg total daily dose in Part A in Study ARV-471-mBC-101, and has almost completed the 700 mg total daily dose level. Data that support the selection of 500 mg QD as a RP2D are as follows:

- No DLTs have been reported with ARV-471 monotherapy among the 45 participants treated in dose escalation and cohort expansion at doses up to 250 mg BID (500 mg total daily dose). In addition, 2 participants have received the 700 mg total daily dose for more than 28 days with no DLT.

- The majority of TRAEs are Grade 1 in severity, with TRAEs in ≥10% of participants limited to nausea, fatigue and arthralgia.

- Except for 1 participant in the 360 mg cohort who discontinued study treatment due to a Grade 3 thromboembolic event that was assessed as possibly related to treatment, there have been no additional Grade 3 TRAEs or treatment discontinuations due to toxicity.

- PK results indicated dose-related increase in exposure (C_{max} and AUC) up to 500 mg dose level.

- The NOAEL in the most sensitive species in nonclinical toxicology studies (female rat) was 100 mg/kg/day, which is equivalent to a human dose of approximately 960 mg. Refer to the IB for details.

- ARV-471 efficacy in participant-derived xenograft models was dose proportional.

No clinically meaningful exposure-response relationship was observed for any safety and efficacy endpoints between the two RP2Ds, except that there is potential risk of QTc prolongation especially in the higher dose group of 500 mg QD based on a 3-month dog toxicology study, concentration-QTc modeling analysis results and preliminary observed dose-dependent increases in QTcF at higher doses of ARV-471 in monotherapy Parts A and B of Study ARV-471-mBC-101. Model-predicted QTcF change from baseline was 6.8 msec (90% CI: 5.7 msec, 7.9 msec) after 200 mg QD and 14.7 msec (90% CI: 12.3 msec, 17.1 msec) after 500 mg QD, respectively, using the observed geometric mean C_{max} for the sum of ARV-471 and ARV-473. No DLTs had been reported across 30 mg to 700 mg total daily doses in Study ARV-471-mBC-101. Based on the totality of the data and benefit-risk profile, the 200 mg QD dose has been selected for the RP3D for the planned Phase 3 ARV-471 monotherapy study. It is considered adequate to evaluate safety and tolerability at the RP3D, 200 mg QD in Phase 1 study in Japanese participants.

In the study, dose escalation beyond 200 mg QD is not planned. If DLT is observed in ≥33% of participants at 200 mg QD, the investigation at the next lower dose level may be explored.

4.3.1. Dose Limiting Toxicity Definition

For purposes of tolerability decisions, a DLT is defined as any AE or abnormal laboratory value which are related to ARV-471 and assessed as unrelated to disease, disease progression, intercurrent illness or concomitant medications/therapies occurring during the first 28 days of treatment that meets at least 1 of the criteria listed in Table 4. A participant is classified as DLT-evaluable if he/she experiences a DLT or in the absence of a DLT, receives at least 75% of the planned dose intensity of study intervention during the DLT window. If a participant does not meet these criteria, he/she may be replaced. All safety information including AEs that have occurred in the participants who were excluded from the DLT evaluation will be considered in the assessment of tolerability. AEs that are clinically significant and considered to be related to the study intervention that occur after the DLT observation period will be reviewed in context of all safety data available. That review may

result in re-evaluation of the dosing level. Severity of AEs will be graded according to CTCAE v5.0.

Table 4. DLT Criteria

Hematological DLTs
• Prolonged myelosuppression, defined as CTCAE Grade ≥3 hematologic parameters (ANC <1000/mm^3, platelet count <50,000/mm^3, or hemoglobin <8 g/dL) in a bone marrow with <5% blasts and no evidence of leukemia or abnormal dysplasia, that lasts longer than 28 days from the point of detection. • Grade ≥3 neutropenia with infection. • Grade 4 neutropenia lasting >5 days. • Febrile neutropenia (defined as an ANC <1.0×10^9/L with a single temperature of >38.3°C or 101°F, or a sustained temperature of ≥38.0°C or 100.4°F for more than 1 hour). • Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion (defined as requiring hospitalization, urgent medical intervention or transfusion). • Grade 4 thrombocytopenia. • Any toxicity requiring dose interruption for ≥14 days will be considered a DLT. Any AE attributed to ARV-471 detected within the DLT evaluation period requiring dose interruption for ≥14 days extending beyond the end of the DLT evaluation period and to post-DLT evaluation period will also be considered a DLT. • Grade 3 leukopenia or neutropenia less than 28 days unaccompanied by fever or infection will NOT be considered a DLT. • Grade 3 thrombocytopenia of less than 28 days without clinical evidence of bleeding will NOT be considered a DLT. • Anemia not requiring transfusion will NOT be considered a DLT. • Any isolated Grade 3 lymphopenia of any duration will NOT be considered a DLT.
Non-Hematologic DLTs
• Grade ≥3 toxicities are DLT. Those that have not been maximally treated and the following AEs will not be considered as DLTs: o Grade 3 nausea/vomiting/diarrhoea or Grade 4 vomiting/diarrhoea lasting <72 hours in the absence of maximal medical therapy. o Grade 3 fatigue lasting less than 7 days. • Hy's Law (concomitant ALT or AST elevation of ≥3×ULN and total bilirubin elevation of ≥2×ULN without a clear alternative etiology) is considered a DLT. • Grade ≥3 electrolyte abnormality that lasts >72 hours, unless the participant has clinical symptoms, in which case all Grade ≥3 electrolyte abnormality regardless of duration should count as a DLT. • Grade ≥3 amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis is NOT considered a DLT. • QTcF prolongation: Any Grade ≥3 QT prolongation must be considered a DLT. The participant must also be evaluated by cardiology and discontinued from the study and study drug. • Any AE attributed to ARV-471 requiring dose interruption for ≥14 days will be considered a DLT. Any AE attributed to ARV-471 detected within the DLT evaluation period requiring dose interruption for ≥14 days extending beyond the end of the DLT evaluation period and to post-DLT evaluation period will also be considered a DLT. • Any death not clearly due to the underlying disease or extraneous causes.

Clinically important or persistent toxicities (eg, toxicities responsible for significant dose delay) that are not included in the above criteria may also be considered a DLT following review by the investigators and the sponsor. To be considered a DLT, the AE must represent a clinically significant shift from baseline and must be considered at least likely related to ARV-471 by the investigator or sponsor.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants (women and men) at least 20 years of age at the time of signing the informed consent.

    - Postmenopausal women due to surgical or natural menopause, defined by at least 1 of the following criteria:

        - Age ≥60 years.

        - Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; **and** follicle-stimulating hormone level within the laboratory's reference range for postmenopausal females.

        - Documented bilateral oophorectomy with surgery at least 2 months prior to start of study treatment.

        - Medically confirmed ovarian failure.

    - Pre- or perimenopausal women or men may be enrolled if treated with an GnRH analogue for at least 4 weeks prior to Cycle 1 Day 1. If a participant has received GnRH analogue, they must remain on it for the duration of the trial.

    - Refer to Section 10.4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Histological or cytological diagnosis of ER+/HER2- advanced breast cancer that is metastatic, recurrent, or locally advanced unresectable breast cancer.

   - ER+ disease must be documented by IHC per ASCO/CAP Guidelines[2].
   - HER2- disease must be documented by either IHC or in-situ hybridization per ASCO/CAP guidelines[3].

3. Participants who are resistant to standard therapy or for which no standard therapy is available or have received;

   - at least 2 prior endocrine regimens in any setting (neoadjuvant, adjuvant or advanced/metastatic). However, the number of prior cytotoxic chemotherapy regimen in the locally advanced or metastatic setting must be no more than 3 regimens.

   All such therapy must be discontinued at least 14 days prior to enrollment.

Informed Consent:

4. Capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Other Inclusion criteria:

5. ECOG PS 0 or 1 (Section 10.12).

6. Adequate Bone Marrow or Coagulation Function, defined as (with no transfusion of blood products or use of hematopoietic growth factors in the 28 days prior to enrollment):

   a. ANC $\geq$1,500/mm^3 or $\geq$1.5 x 10^9/L;

   b. Platelets $\geq$100,000/mm^3 or $\geq$100 x10^9/L;

   c. Hemoglobin $\geq$9 g/dL;

   d. aPTT $\leq$1.25$\times$ ULN and INR $\leq$1.25.

7. Adequate Renal Function, defined as an estimated creatinine clearance $\geq$60 mL/min as calculated using the method standard for the institution.

8. Adequate Liver Function, defined as:

a. Total bilirubin ≤1.5 x ULN (<3 x ULN in a participant with documented Gilbert's syndrome);

b. AST and ALT ≤2.5 x ULN if there is NO liver metastasis; ≤5.0 x ULN if there is liver metastasis.

9. Participants with brain metastases must meet all the following conditions:

   a. Have completed their planned course of treatment;

   b. Have recovered from the acute effects of radiation therapy or surgery prior to first dose of drug;

   c. Have discontinued high-dose corticosteroid treatment for these metastases for at least 4 weeks;

   d. Are neurologically stable as judged by the investigator;

   e. Participants who are diagnosed with a CNS metastasis during the screening period must also meet these criteria.

10. Resolution of acute effects of any prior therapy to either baseline severity or CTCAE version 5.0 Grade ≤1 (except for AEs not constituting a safety risk in the investigator's judgment).

11. Participants must agree and be capable of taking oral medication without crushing, dissolving, or chewing tablets.

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Participants with any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix, Bowen's disease.

2. Participants sustaining major surgery defined as a complex procedure performed under regional or general anesthesia with a recovery period of at least 4 weeks prior to study enrollment.

3. Known or suspected hypersensitivity or severe allergy to active ingredient/excipients of ARV-471.

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

5. Radiation therapy within 4 weeks of first dose of study drug or prior irradiation to >25% of the bone marrow (see Section 10.10 Bone Marrow Reserve in Adults). Palliative radiation for the alleviation of pain due to bone metastasis will be allowed during the study.

Prior/Concomitant Therapy:

6. Concurrent administration of medications, foods or herbal supplements that are strong inhibitors or inducers of CYP3A4 and drugs with a known risk of causing Torsade de Pointes or QT interval prolongation. Prior use of strong CYP3A inhibitors and drugs with a known risk of causing Torsade de Pointes or QT interval prolongation must be stopped 7 days before enrollment and strong CYP3A inducers must be stopped 14 days before enrollment. Refer to Sections 6.8 Concomitant Therapy and 10.8 (Appendix 8).

7. Prior treatment with ARV-471.

8. Systemic anticancer therapy chemotherapy or endocrine therapy within 14 days prior to study entry (6 weeks for mitomycin C or nitrosoureas). If the last immediate anticancer treatment contained an antibody-based agent(s) (approved or investigational), then an interval of 28 days or 5 half-lives (whichever is shorter) of the agent(s) prior to receiving the study intervention treatment is required.

9. Participants who have initiated therapy with bone-modifying agents (bisphosphonates, denosumab, or similar) within 14 days of enrollment (participants who are receiving bone-modifying agents are eligible for this study provided the bone-modifying agent was started more than 14 days prior to study enrollment).

10. Previous high-dose chemotherapy requiring stem cell rescue.

Prior/Concurrent Clinical Study Experience:

11. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry. A participant may be eligible even if they are in the follow-up phase of an investigational study as long as they haven't received treatment in the study for 5 half-lives of the agents.

Diagnostic Assessments:

12. Serum pregnancy test (for females of childbearing potential) positive at screening and/or a breastfeeding participant (including females who are currently breastfeeding or intend to temporarily interrupt breastfeeding).

13. Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) HBV, HCV, and known HIV or AIDS-related illness. Comments regarding specific circumstances follow.

    a. COVID-19/SARS-CoV-2: This protocol excludes participants with active infections, as noted above. While SARS-CoV-2 testing is not mandated for entry into this protocol, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, he/she is excluded.

    b. HIV: In equivocal cases, participants whose viral load is negative may be eligible. HIV seropositive participants who are otherwise healthy and at low risk for AIDS-related outcomes could be considered eligible. Potential eligibility for a specific HIV positive protocol candidate should be evaluated and discussed with the sponsor prior to any screening, based on current and past CD4 and Tcell counts, history (if any) of AIDS defining conditions (eg, opportunistic infections), and status of HIV treatment. Also, the potential for drug-drug interactions will be taken into consideration.

    c. HBV:

        - Participants with active, uncontrolled bacterial, fungal, or viral infection, including HBsAg positive.

        - Participants with positive HBsAb and positive HBcAb are allowed to participate in the study if they have negative HBV DNA test at screening but HB viral load should be monitored for re-activation every 12 weeks.

        - Participants with HBsAb positive who get vaccinated with HBV are exempted from the testing of HB viral load.

        - Participants who test positive for HBV viral load at any time during the study will interrupt administration of ARV-471, and should be considered for consultation with a hepatologist and initiation of antiviral therapies (eg, nucleoside antagonist) in accordance with the JSH Guidelines for the management of Hepatitis B Virus infection.

    d. HCV:

        - Positive HCV antibody is indicative of infection but may not necessarily render a potential candidate ineligible, *(https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf).*

14. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline

QTcF>470 ms, complete LBBB, signs of an acute or indeterminate age myocardial infarction, ST-T interval changes suggestive of active myocardial ischemia, second or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QTcF is >470 ms, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. QTcF exceeds 470 ms, or QRS complex exceeds 120 ms, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS complex values should be used to determine the participant's eligibility. Computer interpreted ECGs should be over-read by a physician experienced in reading ECGs before excluding participants. Cases must be discussed in detail with the sponsor to judge eligibility.

15. Any of the following in the previous 12 months: myocardial infarction, long QT syndrome, Torsade de Pointes, clinically important atrial or ventricular arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), serious conduction system abnormalities (eg, bifascicular block [defined as right bundle branch and left anterior or posterior hemiblock], 3rd degree AV block), unstable angina, coronary/peripheral artery bypass graft, symptomatic CHF, New York Heart Association class III or IV, cerebrovascular accident, transient ischemic attack, symptomatic pulmonary embolism, and/or other clinical significant episode of thrombo-embolic disease. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade (Grade ≥2 in the case of asymptomatic lone atrial fibrillation). If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 ms, the participant may be considered eligible. Participants with cardiac rhythm device/pacemaker must be discussed in detail with the sponsor to judge eligibility.

16. History of symptomatic cardiac valve disease. Participants with mitral valve prolapse which is asymptomatic or not associated with clinically significant sequalae (eg, mitral regurgitation) are eligible. Any case of mitral valve prolapse must be discussed with the sponsor prior to enrollment to confirm eligibility.

17. Active inflammatory gastrointestinal disease, chronic diarrhoea, known diverticular disease or previous gastric resection or lap band surgery.

Other Exclusions:

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

5.3. Lifestyle Considerations

5.3.1. Contraception

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 or her partner(s) from the permitted list of contraception methods (see Section 10.4.4) and will confirm that the participant has been instructed 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) 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 or if pregnancy is known or suspected in the participant or partner.

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. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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 intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to ARV-471.

6.1. Study Intervention(s) Administered

Study Intervention(s)	
Intervention Name	ARV-471
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	100 mg
Dosage Level(s)	200 mg
Route of Administration	Oral
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor Refer to the product specific IP manual.
Packaging and Labeling	Study intervention will be provided in a high-density polyethylene bottle with child-resistant cap. Each bottle will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	NA

6.1.1. Administration

ARV-471 will be administered orally QD with food, in continuous dosing over 28-day cycles.

A participant may continue treatment at the discretion of the investigator until a treatment discontinuation criterion is met (see Section 7.1). Participants who have evidence of radiographic disease progression may be considered for continued study therapy provided the investigator has determined that they are still benefiting from study therapy; this must be reviewed and approved by the sponsor.

Participants will swallow tablet whole, and will not manipulate or chew tablet prior to swallowing.

A cycle is defined as 28 days, regardless of missed doses or dose delays.

Participants should be instructed to take their medication in the morning at approximately the same time each day and to not take more than the prescribed dose at any time.

If a participant misses a day of treatment, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed.

If a participant vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed.

If a participant inadvertently takes 1 extra dose during a day, the participant should not take the next dose of ARV-471.

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions 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 or administer study intervention. 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 for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, 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 definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

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

6. Site staff will instruct participants on the proper storage requirements for takehome study intervention.

7. See the IP manual for storage conditions of the study intervention.

8. The investigator, institution, or the head of the medical institution (where applicable) 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.

9. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

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

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

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention in the bottles provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant should be instructed to maintain the product in the bottle, as appropriate provided throughout the course of dosing and return the bottle, as appropriate to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Participants will be enrolled to the study after participants have given their written informed consent and have completed the necessary baseline (screening visit) assessments. The site staff will email a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a participant ID number and supply this number to the site. The participant ID number will be used on all study-related documentation at the site.

No participant will receive study intervention until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the participant's enrollment;
- Specification of the dose level for that participant and;
- Permission to proceed with dosing the participant.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

6.3.2. Storage

ARV-471 should be stored and shipped at 2°C to 8°C (36°F to 47°F), in a dry place, away from direct sunlight. Do not freeze.

6.4. Study Intervention Compliance

On days of scheduled visits, study drug treatment should be withheld and taken while in the clinic (ie, not at home) under the supervision of study staff. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. Participants will self-dose as described above, with the exception of doses that will be administered at the clinic.

At each visit, prior to dispensing additional study treatment, study center personnel will assess compliance by review of the previously dispensed ARV-471 study treatment in its respective bottle. Participants will be required to return all bottles and remaining tablets of ARV-471, as well as the completed participant diary for drug accountability and documentation of food consumption. Study treatment bottles with unused study treatment may be returned to the participants for continued use. Participants are to complete participant diary daily during study participation. Participants exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen. Noncompliance is defined as taking less than 75% due to reasons other than toxicity or more than 120% of assigned study drug during any evaluation period (visit to visit). Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of ARV-471 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

6.5. Dose Modification

Every effort should be made to administer study intervention on the planned dose and schedule. In the event of significant toxicity, dosing may be delayed and/or reduced as

described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom. In addition to dose modifications, investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Toxicities potentially related to study intervention should be managed according to the dose modifications described in Table 5 and Table 6.

6.5.1. Dose Interruption/Reductions

All treatment-related Grade 3 AEs should have their dose interrupted until return to Grade ≤1 or baseline. Study drug may be resumed using the modification guidelines below (see Table 6).

All treatment-related Grade 4 AEs should have their study treatment discontinued (see Table 6).

No specific dose adjustments are recommended for Grade 1 or 2 treatment-related toxicity. However, investigators should always manage their participants according to their medical judgment based on the particular clinical circumstances.

Participants experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Following dosing interruption or cycle delay due to toxicity, the study intervention dose may need to be reduced when treatment is resumed. Dose reduction of study intervention by 1 dose level (see Table 5) will be allowed depending on the type and severity of toxicity encountered. Participants requiring more than 1 dose reduction will be discontinued from the treatment and entered into the Follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Table 5. Dose Levels

Dose Level	ARV-471
Starting	200 mg/d
-1	100 mg/d

Participants experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved, and in the opinion of the investigator and sponsor, the participant is benefiting from therapy.

Table 6. Dose Reduction

Related Grade 3[a] AEs	ARV-471 Dose Modification[b]
First Dose Reduction	Reduce by 1 dose level[c, d]
Second Dose Reduction	Discontinue ARV-471
Related Grade 4 AE	**Discontinue ARV-471[e]**

Table 6. Dose Reduction

Related Grade 3[a] AEs	ARV-471 Dose Modification[b]

a. Grade 3 AEs not requiring dose reduction:
Grade 3 fatigue lasting <7 days;
Grade 3 lymphopenia lasting <72 hours;
Grade 3 nausea/vomiting/diarrhoea lasting <72 hours in the absence of maximal medical therapy.
b. See Table 5.
c. Depending on the nature of the toxicity and the rapidity of recovery following dose interruption, resumption of the same dose may be considered after the first instance of the related Grade 3 AE.
d. If the participant has demonstrated significant benefit, the AE was rapidly reversible, and redosing is not expected to pose a significant risk to the participant, dose re-escalation of ARV-471 may be considered after consultation with the sponsor.
e. If the participant has demonstrated significant benefit, the AE was rapidly reversible, and redosing is not expected to pose a significant risk to the participant, resumption of ARV-471 at a reduced dose may be considered dependent on the nature of the Grade 4 AE after consultation with the sponsor.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

ARV-471 treatment should be permanently discontinued for any dosing interruption lasting >28 days with the following exceptions:

- Dosing interruptions >28 days that occur for non-drug-related reasons may be allowed if approved by the sponsor. Prior to re-initiating treatment in a participant with a dosing interruption lasting >28 days, the sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

6.6. Continued Access to ARV-471 After the End of the Study

No intervention will be provided per protocol to study participants beyond the end of the study.

6.7. Treatment of Overdose

For this study, any dose of ARV-471 that is ≥150% of the planned dose within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or qualified designee should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of ARV-471 (whichever is longer).

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

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

5. Obtain a blood sample for PK analysis within 7 days from the date of the last dose of ARV-471 if requested by the sponsor (determined on a case-by-case basis).

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

6.8. Concomitant Therapy

All prior and concomitant treatments, received by participants from screening and up to 28 days after the last dose of study treatment, or up to the start of new anticancer therapy, including supportive care drugs (eg, anti-emetic treatment and prophylaxis), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, transfusions) will be recorded on the CRF. Concomitant medications for AEs and SAEs should follow respective guidance for the AE and SAE reporting period. Only subsequent anticancer therapy initiated after end of study treatment(s) will be reported at the follow-up visits.

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician.

Palliative radiotherapy on study is permitted (eg, skeletal administration for mBC), but should be discussed with the sponsor prior to initiation. Bisphosphonates and RANKL inhibitors are allowed. Paracetamol/acetaminophen at doses of ≤2 g/day is permitted for use any time during the study. Herbal supplements and Chinese herbal medicines are not permitted, if the ingredients are unknown or included ingredients may have potential DDI (refer to Section 10.8). Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the sponsor, as necessary.

6.8.1. Prohibited Medications/Therapy

Other therapies with known anticancer effects are prohibited during study participation. Ovarian suppression therapy with GnRH agonists is not considered anticancer therapy and is allowed.

Medications which are not allowed in this study refer to Section 10.8.

6.8.2. Proton Pump Inhibitors

Co-administration of gastric acid-reducing agents may reduce ARV-471 absorption. The concomitant use of PPIs with ARV-471 is not recommended. If PPI treatment is required, ARV-471 intake with a moderate-fat meal (400-800 calories, approximately 35% fat) is recommended. Refer to Section 10.8 for examples of drugs that are PPIs.

6.8.3. H_2 Receptor Antagonists or Antacids

H_2 receptor antagonists (eg, cimetidine, famotidine, etc.) or local antacids (eg, aluminum hydroxide, calcium carbonate, bismuth subsalicylate, etc.) may be used, but should be

staggered. Administer ARV-471 ≥2 hours before or after antacids. Administer ARV-471 ≥2 hours before or 10-12 hours after H_2 receptor antagonists.

6.8.4. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current ASCO guidelines.

6.8.5. Hematopoietic Growth Factors and Transfusions

Primary prophylactic use of colony stimulating factors is not permitted during the first 28 days of Cycle 1, but they may be used to treat treatment-emergent neutropenia or participants experienced DLT in Cycle 1 as indicated by the current ASCO guidelines[9] or Japanese package insert. During the screening window (ie, 28 days prior to Day 1), Granulocyte colony stimulating factors are not permitted to qualify a participant with low WBC counts.

Packed red blood cell and platelet transfusions should be administered only if clinically indicated. These treatments are not permitted during the first 28 days of Cycle 1, but may be used for participants experienced DLT in Cycle 1.

6.8.6. Antidiarrheal, Antiemetic Therapy

Primary prophylaxis beyond the first cycle is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected DDI and assuming the drug is not included in the Concomitant Therapy section (Section 6.8).

6.8.7. Corticosteroids

Chronic systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

6.8.8. Surgery and Radiotherapy

Caution is advised for any surgical procedures during the study. The appropriate interval of time between surgery and ARV-471 required to minimize the risk of impaired wound healing and bleeding has not been determined. Postoperatively, the decision to reinitiate ARV-471 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery. Palliative radiotherapy to specific sites of disease will be permitted if considered medically necessary by the treating physician. All attempts will be made to rule out progressive disease in the event of increased localized pain.

7. DISCONTINUATION OF ARV-471 AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of ARV-471

It may be necessary for a participant to permanently discontinue ARV-471. Reasons for permanent discontinuation of study intervention may include the following:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death;

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety follow-up. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

See Section 10.9.4 for guidance for participants with active or presumed SARS-CoV-2 infection.

Follow-Up:

At least 28 calendar days, and no more than 35 calendar days after discontinuation of study intervention, participants will return to undergo review of concomitant treatments, brief physical examination, ECOG PS and assessment for AEs and SAEs. Participants continuing to experience AEs at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

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 may include:

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

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

If a participant withdraws from the study, he/she 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 should be performed and no additional data should 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 him or her 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 he or she 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, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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 may 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 he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

During the COVID-19 pandemic, please refer to Section 10.9 for safety and efficacy assessments.

8.1. Efficacy Assessments

8.1.1. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging will include contrast enhanced chest, abdomen and pelvis computed tomography or MRI scans; brain computed tomography or MRI scan for participants with known or suspected brain metastases; bone scan and/or bone x-rays for participants with known or suspected bone metastases. For participants with known computed tomography contrast allergy, a non contrast computed tomography of the chest with contrast enhanced abdominal and pelvic MRI can be used. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the SoA, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 8 weeks or 12 weeks [as applicable]). Assessment of response will be made using RECIST version 1.1 (see Section 10.11).

All participants' files and radiologic images must be available for source verification.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

PE 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.

ECOG PS will also be measured and recorded as per the SoA. ECOG performance scale is available in Section 10.12.

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 (Section 10.3) must be reported according to the processes in Section 8.3.1 to 8.3.3.

8.2.2. Vital Signs

Oral, tympanic, axillary or skin temperature, pulse rate, respiratory rate, and BP will be assessed.

BP and pulse rate measurements will be assessed in a sitting or semi-recumbent position (the same position should be maintained throughout the study) with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded on the CRF.

8.2.3. 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, QT, and QTcF intervals and QRS complex. For ECG machines that do not report QTcF, calculation of QTcF from QT and HR, for example using online tools, is permitted. 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.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >500 msec; or b) an absolute QT value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted

if QTcF intervals 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 QTcF 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 Section 10.7.

8.2.4. Echocardiograms

A screening echocardiogram is required with special attention to valvular structure and function. A multigated acquisition scan is not sufficient. An echocardiogram should be repeated as clinically indicated.

8.2.5. Clinical Safety Laboratory Assessments

See Section 10.2 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 Section 10.2, 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 relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which 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 significantly 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 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 Section 10.6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be

commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the ARV-471. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

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

The definitions of an AE and an SAE can be found in Section 10.3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant/ legally authorized representative 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.

8.3.1. 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 the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers 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.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 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 Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

8.3.1.2. 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 8.3.1, 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.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. 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 Section 10.3.

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.

8.3.3. 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 given in Section 10.3.

8.3.4. 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.

8.3.5. 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 exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. 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 exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to 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 exposes 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 a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 30 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until

completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion;
- 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.

8.3.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female 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 accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.3.5.3. 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.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

The following DREs are common in participants with ER+/HER2- locally advanced or mBC and can be serious/life threatening:

- Disease progression

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the corresponding CRF page in the participant's CRF within the appropriate time frame.

Note: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. 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.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include, but are not limited to:

- 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.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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.

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

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.

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

8.4. Pharmacokinetics

Blood samples (4 mL) to provide a minimum of 1.5 mL for measurement of plasma concentrations of ARV-471 and ARV-473, will be collected into appropriately labeled tubes 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.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. If a scheduled blood sample collection on and after Cycle 2 (except for Cycle 1) cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

With regard to serial PK sampling on Cycle 1 Days 1 and 15, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) 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.

For pre-dose samples on Cycle 1 Days 2, 8, 16 and 22, Cycle 2 Days 1 and 15, and Cycle 3 Days 1 and 15, pre-dose samples collected within 24 hours ± 10% (ie, 2 hours and 24 minutes) after the dose administration on the day prior to the pre-dose PK sampling AND collected prior to administration of ARV-471 on that day (for pre-dose PK samples) will be considered protocol compliant. Participants must be instructed to withhold their daily dose of study drugs on PK sampling days until the pre-dose PK sample collection has been completed. The actual date and time (24-hour clock time) of the sample collection and the most recent dosing date and time before and after each collection will be recorded on the CRF. The actual times may change, but the number of samples will remain the same. The date of missing dose should be also be recorded in the CRF.

C_{trough} at steady state is defined as the pre-dose concentration that meets the following dose-compliant acceptance criteria:

- Participants must have received 6 consecutive days at the same dose of ARV-471 once daily prior to the pre-dose PK sampling;
- PK samples must have been collected 24 hours ± 10% after the dose administered the day prior to the pre-dose PK sampling.

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. All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

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.

As part of understanding the PK of the investigational product, samples may be used for metabolic identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the CSR.

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.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. 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 a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

There are no statistical hypotheses in this study so that no formal statistical testing will be performed.

9.1.1. Estimands

9.1.1.1. DLT

The estimand is defined by the following attributes:

Population: participants who receives at least 1 dose and classified as DLT-evaluable, ie, participants who experiences a DLT or in the absence of a DLT, receives at least 75% of the planned dose intensity of study intervention during the DLT window.

Endpoint: occurrence of DLTs at first cycle. For the definition of DLTs, see Section 4.3.1.

Treatment condition: Participants who fail to complete at least 75% of study drug treatment in Cycle 1 for reasons other than DLT (eg, logistical or technical reasons, non-DLT-related dose delays) are considered not to be DLT-evaluable and will be replaced.

Population-level summary: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants in the DLT-evaluation period.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full Analysis Set (FAS)	All enrolled participants who have been assigned to treatment. Participants are analyzed according to the treatment they were assigned.
Safety Analysis Set (SAS)	All enrolled participants who receive at least 1 dose of study intervention. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses.
DLT Evaluable Set	All enrolled participants who receive at least 75% of the planned dose intensity of study treatment and either experienced DLT or do not have major protocol deviations during the DLT observation period.
PK Parameter Set	All enrolled participants treated who do not have protocol deviations influencing PK assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest.

Participant Analysis Set	Description
PK Concentration Set	All enrolled participants who are treated and have at least 1 analyte concentration above the lower limit of quantitation.
Response Evaluable Set	All enrolled participants who received at least one dose of study treatment and had adequate baseline disease assessment. Participants who discontinued early or died will be included.
PD/Biomarker Analysis Set(s)	The PD/Biomarker analysis population is defined as all enrolled participants with at least 1 of the PD/Biomarkers evaluated at pre and/or post dose.

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. General Considerations

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, PK measurements, and biomarker measurements.

9.3.2. Primary Endpoint(s)/Estimand(s)/Analysis

The first cycle DLT is the primary endpoint of this study. The occurrence of DLTs observed in the dosing cohort in Japanese population is used to confirm the tolerability of the RP3D that was determined in Study ARV-471-mBC-101 conducted outside Japan. The target DLT rate is 33%. If a proportion of observed DLTs in this study is less than 33%, the tolerability of the RP3D in Japanese population is considered to be confirmed. AEs constituting DLTs will be listed. Confirmation of the tolerability of the RP3D will be performed using the DLT evaluable set.

If there is either no or 1 DLT in 6 participants, the tolerability of the RP3D is confirmed. If 2 of 6 participants experience DLT, an additional 3 participants can be enrolled or the next lower dose level can be explored to further investigate the safety and tolerability of ARV-471 as monotherapy in Japanese participants. If no DLT is reported in an additional 3 participants, the RP3D will be considered tolerable in Japanese participants. If DLT is observed in ≥33% of participants at 200 mg QD, the investigation at the next lower dose level may be explored.

9.3.3. Secondary Endpoint(s)/Estimands Analysis

9.3.3.1. Adverse Events

AEs will be graded by the investigator according to the NCI CTCAE version 5.0 and coded using MedDRA. AE data will be reported in tables and listings. Summaries of AE by appropriate MedDRA terms, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death and premature withdrawal from study treatment. The number and percentage of participants who

experienced any AE, SAE, TRAE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs on the entire study period. Listings of DLTs and deaths will be provided.

9.3.3.2. Laboratory Test Abnormalities

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests on the entire study period. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.3.3.3. Pharmacokinetic Analysis

The concentrations of ARV-471 and ARV-473 will be summarized by descriptive statistics (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and geometric CV) by cycle, day and nominal time. Individual participant, median and mean profiles of the concentration-time data will be plotted by cycle and day (single dose and steady state) using nominal times. Individual, median and mean profiles will be presented on both linear-linear and log-linear scales.

All the concentration data will be listed but the concentrations deviated more than 10% from the planned time will not be included in summarization.

Plasma PK parameters for ARV-471 and ARV-473 following multiple dose administration will be derived from the concentration-time profiles using noncompartmental methods as data permit. The PK parameters to be assessed in this study, their definition, and method of determination are outlined in Table 7. In all cases, actual PK sampling times will be used in the derivation of PK parameters. The single-dose PK parameters on Day 1 in Cycle 1 and steady-state PK parameters on Day 15 in Cycle 1 will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and geometric CV) by cycle and day.

C_{trough} at steady state will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and geometric CV) by cycle and day. C_{trough} at steady state will be plotted by cycle and day, and also plotted using a box whisker plot by cycle and day. C_{trough} at steady state is defined as the pre-dose concentration that meets the following dose-compliant acceptance criteria:

- Participants must have received 6 consecutive days at the same dose of ARV-471 once daily prior to the pre-dose PK sampling;
- PK samples must have been collected 24 hours ± 10% after the dose administered the day prior to the pre-dose PK sampling.

Table 7. Definition of Plasma Pharmacokinetic Parameters for ARV-471 and ARV-473

Parameter	Day 1 (D1) or Day 15 (D15)	Definition	Method of Determination
C_{max}	D1 & D15	Maximum observed plasma concentration	Observed directly from data
T_{max}	D1 & D15	Time to reach C_{max}	Observed directly from data as time of first occurrence
AUC_{last}	D1 & D15	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{tau}	D1 & D15	Area under the plasma concentration-time curve from time zero to time tau (τ), the dosing interval, where tau = 24 hours (QD dosing)	Linear/Log trapezoidal method
C_{min}	D15	Lowest concentration observed during the dosing interval	Observed directly from data
C_{trough}	D15[c]	Pre-dose plasma concentration during multiple dosing	Observed directly from data
$t_{½}$[a]	D1 & D15	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el}[d] was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
$t_{½eff}$	D15	Effective half-life ($t_{½eff}$) based on R_{ac}	$t_{½eff}$=tau*ln2/ln[R_{ac}/(R_{ac}-1)]
CL/F[b]	D15	Apparent clearance	Dose/AUC_{tau}
Vz/F[a,b]	D15	Apparent volume of distribution	Dose/(AUC_{tau}*k_{el})
MRC_{max}	D1 & D15	ARV-473 to ARV-471 ratio for C_{max}	C_{max} for ARV-473/C_{max} for ARV-471
$MRAUC_{tau}$	D1 & D15	ARV-473 to ARV-471 ratio for AUC_{tau}	AUC_{tau} for ARV-473/ AUC_{tau} for ARV-471
R_{ac}	D15	Accumulation ratio based on AUC (observed)	$AUC_{tau,D15}$ /$AUC_{tau,D1}$

a. If data permit.
b. ARV-471 only.
c. C_{trough} will be evaluated on Days 15, 16 and 22 of Cycle 1 and Days 1 and 15 of Cycle 2 and 3, if data permit.
d. The terminal phase rate constant, kel, is estimated as the absolute value of the slope of a linear regression during the terminal phase of the natural-logarithm (ln) transformed concentration-time profile. Terminal half-life and other parameters based on kel should only be reported when the terminal phase is well characterized. The detailed criteria considered will be included in the SAP.

9.3.3.4. Antitumor activities

The response evaluable set will be used for all response-related analysis. Tumor response will be presented in the form of participant data listings that include, but are not limited to, tumor type, tumor response at each visit, and BOR. In addition, progression date, death date,

date of first response and last assessment date, and date of last contact will be listed. A summary of tumor response and BOR based on RECIST version **1.1** will also be presented.

The detailed analyses will be described in the SAP.

Best Overall Response

BOR will be assessed based on RECIST version **1.1.**

ORR is defined as the percentage of participants with a BOR of CR and PR. The ORR and its exact 95% CI will be summarized using Wilson's score methodology.

The CBR is defined as the percentage of pa1iicipants with BOR of CR, PR and SD of 24 weeks duration or longer. The CBR and its exact 95% CI will be summarized using Wilson's score methodology.

For analyses of ORR and CBR, paiiicipants with confmned and unconfnmed responses will be included as responders. A summaiy table ofBOR will also be provided. For these analyses, confnmed and unconfnmed responses will be summai·ized separately.

Progression Free Survival

PFS is the time from the first date of the study intervention to the date of the first documentation of progression, or death due to any cause. Progression is defined as the appeai·ance of local, regional or distant disease of the same type after CR or progression of pre-existing lesions. The Kaplan-Meier method will be used to analyze PFS. A data listing of PFS will be provided.

Duration of Response

DOR is defined for participants with confnmed objective response (as defined above in overall response) as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. The Kaplan-Meier method will be used to analyze DOR, if appropriate. A data listing of DOR will be provided. DOR for participants with unconfmned objective response will also be summai·ized sepai·ately.

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9.3.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, cardiac monitoring results, 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.

9.3.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time.

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

Safety QTcF Assessment

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

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point for summarization and categorical analysis. If any of the 3 individual ECG tracings at each time point 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. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the timematched baseline triplicate values on Day 1, or the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between exposure and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

The analysis of ECG results will be based on participants in the SAS with baseline and on-treatment ECG data. Baseline ECG is defined as the most recent ECG prior to Cycle 1 Day 1 dosing.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will QTcF using standard conection factors (ie, Fridericia's [default conection], Bazett's, and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT interval, HR, RR interval, PR interval, QRS complex, QTcF, and by dose. Individual QT intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of centrnl tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute value of the QTc interval and changes from baseline in QTc after treatment, by dose and time point. Details of additional analysis (if any) will be specified in SAP.

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9.4. Interim Analyses

No fonnal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or suppo1iing clinical development.

9.5. Sample Size Determination

Six paiiicipants will be enrolled to evaluate DLT and an additional 3 paiiicipants may be enrolled depending on the number of paiiicipants with DLTs (total up to 9 paiiicipants). Paiiicipants who fail to complete at least 75% of study dmg treatment in Cycle 1 for reasons other than DLT are considered not to be DLT-evaluable and will be replaced. If 2 DLTs occur in 6 paiiicipants, the investigator and the sponsor should discuss the safety and tolerability based on the available data, and then under the agreement between the investigator and the sponsor, it may be allowed to enroll an additional 3 pa1iicipants at the same dose level. Or, if DLT is observed in 2 of 6 paiiicipants at 200 mg QD, the investigation at the next lower dose level may be explored. Thus, the actual sample size may depend on the underlying dose toxicity profile. The RP3D is considered intolerable in Japanese paiiicipants if 33% DLTs are observed in this study. Although the sample size is not based on any statistical considerations, the sample size of 6 pa1iicipants would have 57.98% chance to declai·e that the RP3D determined in Study ARV-471-mBC-101 has

exceeded the MTD for Japanese participants if the true DLT rate for Japanese participants is 30% and over (Table 8). Similarly, the sample size of 6 would have 76.67% and 89.06% chance to detect probability of over MTD if the true DLT rate is 40% and 50%, respectively.

Table 8. Detection Probability of Over MTD

Number of DLTs Observed		True DLT Rate									
Total Sample Size	Total	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
6	0-1	96.72	88.57	77.65	65.54	53.39	42.02	31.91	23.33	16.36	10.94
	2	3.05	9.84	17.62	24.58	29.66	32.41	32.80	31.10	27.80	23.44
	≥3	0.22	1.59	4.73	9.89	16.94	25.57	35.29	45.57	55.85	65.63
9[a]	2[b]	2.62	7.17	10.82	12.58	12.51	11.12	9.01	6.72	4.62	2.93
	≥3[b]	0.44	2.67	6.80	11.99	17.15	21.30	23.79	24.39	23.17	20.51
Detection Probability of Over MTD with Sample Size of 6		3.28	11.43	22.35	34.46	46.61	57.98	68.09	76.67	83.64	89.06
Detection Probability of Over MTD with Sample Size of Up to 9[a]		0.66	4.25	11.53	21.88	34.09	46.86	59.08	69.95	79.02	86.13

a: An additional 3 participants will be allowed based on agreement between the investigator and sponsor only if 2 DLTs occur in the initial 6 participants. If 3 or more DLTs occur in the initial 6 participants, it is considered as over MTD and not allowed an additional participants.
b: The sum of 2 DLTs that occurred in the initial 6 participants and the DLT that occurred in an additional 3 participants.

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 (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), 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 that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative 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 or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative 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 or his or her legally authorized representative must be informed that his/her 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 or his or her legally authorized representative.

The participant or his or her legally authorized representative must be informed that his/her 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 or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

Participants or his or her legally authorized representative must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a 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, and/or www.pfizer.com, and other public registries 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 participants) 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

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

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 available from these trials 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 redacted.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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 the 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.

Definition of what constitutes source data and its origin can be found in the Clinical Monitoring Plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

Study monitors will perform ongoing source data verification 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, the 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. 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 or designee/CRO 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.

If the sponsor decides to terminate the study for a reason unrelated to the safety of study intervention(s), participants may continue to receive study intervention(s) per the investigator's judgement and protocol-specified safety assessments will continue to be performed for these participants until the end of study as defined in Section 4.4. The following non-safety-related study procedures and assessments may be stopped upon written notification from the sponsor:

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

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

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

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

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

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

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

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Pfizer internal system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, 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 ID number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Assessments

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 9. Core Lab Tests

<table>
<tr><th>Hematology</th><th>Coagulation</th><th>Pregnancy Test</th><th>Notes</th></tr>
<tr><td>Hemoglobin</td><td>PT or INR</td><td rowspan="4">For female participants of childbearing potential, on serum or urine (to be specified in the protocol</td><td rowspan="16">Database should be constructed to allow capture of differential counts as percent and absolute values but only one or the other should be used by the site to collect data. Results will be reported as absolute values after conversion and graded according to the CTCAE criteria</td></tr>
<tr><td>Platelets</td><td>PTT or aPTT</td></tr>
<tr><td>WBC</td><td></td></tr>
<tr><td>Absolute Neutrophils</td><td>Serology</td></tr>
<tr><td>Absolute Lymphocytes</td><td>HBV*</td><td></td></tr>
<tr><td>Absolute Monocytes</td><td>HCVAb*</td><td>Urinalysis</td></tr>
<tr><td>Absolute Eosinophils</td><td>HIV/HIVAb*</td><td rowspan="6">Urine dipstick: pH, Glucose, Protein, Blood, Ketones, Nitrites, Leukocyte esterase, Urobilinogen, Urine bilirubin
For urine protein, if dipstick shows urine protein ++ or above, perform 24-hour urine protein test.
Only if urine dipstick is positive for blood, protein, nitrates or leukocyte esterase, perform microscopy (Reflex Testing).</td></tr>
<tr><td>Absolute Basophils</td><td></td></tr>
<tr><td></td><td>Endocrinology</td></tr>
<tr><td>Chemistry</td><td>TSH</td></tr>
<tr><td>ALT</td><td rowspan="3"></td></tr>
<tr><td>AST</td><td></td><td></td></tr>
<tr><td>Alk Phos</td><td></td><td></td></tr>
<tr><td>Sodium</td><td></td><td></td><td></td></tr>
<tr><td>Potassium</td><td></td><td></td><td></td></tr>
<tr><td>Magnesium</td><td></td><td></td><td></td></tr>
<tr><td>Chloride</td><td></td><td></td><td></td></tr>
<tr><td>Total Calcium</td><td></td><td></td><td></td></tr>
<tr><td>Total Bilirubin**</td><td></td><td></td><td></td></tr>
<tr><td>BUN or Urea</td><td></td><td></td><td></td></tr>
<tr><td>Creatinine</td><td></td><td></td><td></td></tr>
<tr><td>Uric Acid</td><td></td><td></td><td></td></tr>
<tr><td>Glucose (non-fasted)</td><td></td><td></td><td></td></tr>
<tr><td>Albumin</td><td></td><td></td><td></td></tr>
<tr><td>Phosphorus or Phosphate</td><td></td><td></td><td></td></tr>
<tr><td>CK</td><td></td><td></td><td></td></tr>
<tr><td>Amylase</td><td></td><td></td><td></td></tr>
</table>

Table 9. Core Lab Tests

Lipase			

* HBsAg, HBsAb, HBcAb, HBV DNA, HCVAb, and HIV/HIVAb to be conducted by local laboratory where required by local regulations or if warranted by participant history
**For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, and ALP.

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.

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 occmTence in a paiiicipant or clinical study paiticipant, 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 abnonnal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abno1mal laborato1y test results (hematology, clinical chernistiy, 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 abno1mal 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 drng tl'eatment, or other therapy.
 	
• Exacerbation of a chronic or intennittent preexisting condition, including either an increase in 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 staii of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected DDI.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be repo1ied as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-haiming intent. Such overdoses should be repo1ied regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnonnal laborato1y findings or other abnonnal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiiicipant'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 paiiicipant'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 occunence 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 staii of the study that do not worsen.
- Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be repo1ied as AEs.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The te1m "life-threatening" in the definition of "serious" refers to an event in which the paiiicipant 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 pa1iicipant has been detained (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 ai·e AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occmTed or was necessaiy, 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, diarrhoea, 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, is considered serious. 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 but 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. • Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Severity section).

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 breastfeeding **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 non-participant (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 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 Severity

The investigator will make an assessment of severity for each AE reported during the study and assign it to 1 of the categories listed below (as defined by the NCI CTCAE system). 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.

GRADE	Clinical Description of Severity
1	MILDAE
2	MODERATEAE
3	SEVEREAE
4	LIFE-THREATENING; urgent intervention indicated
5	DEATH RELATED TO AE

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 his/her assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has 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 his/her 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.

- 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 infonnation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primaiy mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electrnnic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entiy of new data or changes to existing data.
- If a site receives a repo1t of a new SAE from a study paiticipant or receives updated data on a previously repo1ted SAE after the electi·onic data collection tool has been taken off-line, then the site can repo1t this infonnation on a paper SAE fonn (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsiinile ti·ansinission of the CT SAE Repo1t Fo1m is the prefened method to ti·ansinit this info1mation to Pfizer Safety.
- In circumstances when the facsiinile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Fonn sent by overnight mail or com-ier servïce.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Repo1t Fo1m pages within the designated repo1ting 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 30 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential 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 woman of childbearing potential 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

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 30 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 30 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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 and Non-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 <u>not</u> 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 an alternate 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 of age and not using hormonal

contraception or HRT. When there is a high FSH level, it should be confirmed that there is no other medical cause.

- A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they 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.

Highly Effective Methods That Have Low User Dependency

1. Intrauterine device.
2. Bilateral tubal occlusion.
3. Vasectomized partner.

    - A 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

1. 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.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- 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).

* not approved in Japan.


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10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are “adaptors” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili 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 TBili 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 TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an ALP value <2 × ULN or not available.

For participants with baseline AST **OR** ALT **OR** TBili 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 TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili 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 TBili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and ALP. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili 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: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AE
• 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 ati·ial flutter or fibrillation, with conu-olled venti·icular RR: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of>30 seconds' duration. • Frequent PVCs, ti·iplets, or sho1t intervals (<30 seconds) of consecutive venti·icular complexes.
ECG Findings That May Qualify as Serious AE

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS >120 ms).
• New-onset right bundle branch block (QRS >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free paiticipants 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 paiticipants with au-ial fibrillation and bradycai·dia with 1 or more pauses of at least 5 seconds or longer.
  • Au-ial flutter or fibrillation, with rapid venti·icular RR: rapid= rate >120 bpm.
• Sustained supraventi·icular tachycardia (rate>120 bpm) ("sustained"= sho1t duration with relevant symptoms or lasting>1 minute).
• Venti·icular rhythms >30 seconds' duration, including idioventi·icular rhythm (HR <40 bpm), accelerated idioventi·icular rhythm *(HR* >40 bpm to <l 00 bpm), and

monomorphic/polymo1phic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

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

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infai·ction.
- Sustained ventriculai·tachyaiThythmias (>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 atThythmia classified as an adverse expenence.

The enumerated list of major events of potential clinical concem are recollllllended as "ale1ts" or notifications from the core ECG laborato1y to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Prohibited Concomitant Medications That May Result in DDI

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

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

10.8.1. CYP3A inhibitors/inducers

The concurrent use of the following treatments **is prohibited** throughout the duration of the active treatment phase.

- CYP3A accounted for 85% of the CYP metabolism of ARV-471 based on *in vitro* data. Co-administration with drugs that are strong CYP3A inhibitors and inducers may change the plasma concentrations of ARV-471 in humans.
- The concurrent use of strong CYP3A inhibitors/inducers is prohibited throughout the duration of the active treatment phase. Additionally, the concurrent use of herbal supplements and Chinese herbal medicines are not permitted, if the ingredients are unknown or included ingredients may have potential DDI such as strong CYP3A inducers or inhibitors.

Prior use of medications, food, herbal supplements, Chinese herbal medicines that are strong inhibitors of CYP3A must be stopped 7 days before enrollment. Strong inducers of CYP3A must be stopped 14 days before enrollment.

Examples of prohibited concomitant medications are provided below.

This is not an all-inclusive list (examples including, but not limited to the drugs provided below).

Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Investigators should consult the product prescribing information for any other medication used throughout the duration of the active treatment phase for information regarding medication that is prohibited for concurrent use.

Table 10. List of CYP3A Inhibitors/Inducers

Drug Category	Drugs
Strong CYP3A inhibitors*	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir, elvitegravir, josamycin, indinavir, itraconazole, ketoconazole, lopinavir, lonafamib, mibefradil, mifepristone, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir, telaprevir, troleandomycin, tipranavir, telithromycin, voriconazole, grapefmit, grapefmit juice or any product containing izrapefmit
Strong CYP3A inducers*	apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, mitotane, phenvtoin, rifampin, rifapentine and St. John's WOii

* Dmg-Dmg Interaction Database (DIDB, 2022) provided by University of Washington and Food and Dmg Administration listings (FDA, 2020) as sources:

- DIDB[10]: https://www.drnginteractionsolutions.org/
- FDA[11]: https://www.fda.gov/drngs/drng-interactions-labeling/dmg-development-and-drng-interactions-table-substrates-inhibitors-and-inducers

10.8.2. Drugs Known to Predispose to Torsade de Pointes or QT interval prolongation

The relationship between ARV-471 concentration and QT/QTc interval is unknown. Regarding the detailed info1mation, refer to Section 2.3. Concunent use of ARV-471 with diugs of known risk of causing Torsade de Pointes or QT interval prolongation is prohibited throughout the duration of the active treatment phase.

This is not an all-inclusive list (examples including, but not limited to the diugs provided below).

Table 11. List of Drugs Known to Predispose to Torsade de Pointes

Drug Category	Drugs
Drugs known to predispose to Torsade de Pointes*	aclambicin, amiodarone, anagrelide, arsenic trioxide, astemizole*, azithromycin, bepridil, cesium chloride*, chloroquine, chlorpromazine, chlorprothixene*, cilostazol, ciprofloxacin, cisapride*, citalopram, clarithromycin, disopyramide, dofetilide*, domperidone, donepezil, dronedarone*, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin*, grepafloxacin*, halofantrine*, haloperidol, hydi·oquinidine*, hydi·oxychloroquine, ibogaine*, ibutilide*, levofloxacin, levomepromazine (methotrimeprazine), levomethadyl*, levosulpiride*, meglumine antimoniate*, mesoridazine*, methadone, moboce1iinib*, moxifloxacin, nifekalant, ondansetron, oxaliplatin, papaverine HCl (intra-corona1y), pentamidine, pimozide, probucol, procainamide, quinidine, roxithromycin, se1iindole*, sevoflurane, sotalol, sparfloxacin*, sulpiride, sultopride, terfenadine*, terlipressin*, terodiline* thioridazine*. vandetanib

*Dmgs are not launched or was removed from Japan market (gatifloxacin: ophthalmic chug is only launched)

Adapted from crediblemeds.org (organization that curates the University of Arizona Cancer Center for Education and Research on Therapeutics database: "Risk Categories for Drugs that Prolong QT & induce TdP-Known Risk of TdP".
See website for current list: https://crediblemeds.org/index.php/druglist

10.8.3. Substrates of Transporters

ARV-471 is an in vitro inhibitor of P-gp and BCRP. Treatment with ARV-471 has potential for increasing exposure of concomitant medications that are substrates for P-gp and BCRP transporters. P-gp substrates should be used **with caution**. BCRP substrates, rosuvastatin and sulfasalazine, may be used because safety risk is low.

This is not an all-inclusive list (examples including, but not limited to the drugs provided below).

Table 12. List of P-gp Sensitive Substrates

Drug Category	Drugs
P-gp sensitive substrates*	dabigatran etexilate, digoxin/digitoxin, fexofenadine

* Drug-Drug Interaction Database (DIDB, 2022) provided by University of Washington and Food and Drug Administration listings (FDA, 2020) as sources:

- DIDB[10]: https://www.druginteractionsolutions.org/
- FDA[11]: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

10.8.4. PPI

Co-administration of PPIs may reduce ARV-471 absorption. The concomitant use of PPIs with ARV-471 is not recommended.

This is not an all-inclusive list (examples including, but not limited to the drugs provided below).

Table 13. List of Proton Pump Inhibitors

Drug Category	Drugs
Proton pump inhibitors (PPIs)*	esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole**, dexlansoprazole**

* Refer to corresponding concomitant drugs USPIs or local product prescribing information.
** Drugs are not launched in Japan.

10.9. Appendix 9: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic in Japan and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.9.1. Eligibility

While SARS-CoV-2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if he/she has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV-2. Participants with active infections are excluded from study participation as per Exclusion Criterion 13a. When the infection resolves, the participant may be considered for re-screening.

10.9.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 10.4 and Section 10.9.3.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.9.3. Alternative Facilities for Safety Assessments

10.9.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology;
- Chemistry;
- Coagulation;
- Urinalysis;
- Pregnancy test;
- Endocrinology;
- Serology.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.9.3.2. Imaging

If the participant is unable to visit the study site for safety imaging assessment(s), the participant may visit an alternative facility to have the safety imaging assessment(s) performed. Qualified study site personnel must order, receive, and review results.

10.9.3.3. Electrocardiograms and Echocardiogram

If the participant is unable to visit the study site for ECGs and echocardiogram, the participant may visit an alternative facility to have the ECGs and echocardiogram performed. Qualified study site personnel must order, receive, and review results.

10.9.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

ARV-471 may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the ARV-471. Pfizer does not permit the shipment of ARV-471 by mail. The tracking record of shipments and the chain of custody of ARV-471 must be kept in the participant's source documents/medical records.

The following is recommended for the administration of ARV-471 for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV-2 infection:

- For symptomatic participants with active SARS-CoV-2 infection, ARV-471 should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV-2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV-2-related symptoms should have recovered to Grade ≤1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to consider potential drug-drug interactions as described in Section 6.8 for any concomitant medication administered for treatment of SARS-CoV-2 infection

10.9.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- PE;

- Vital Signs (including height and weight);

- ECOG;

- Safety laboratory blood draws (including hematology, chemistry, coagulation, endocrinology, serology);

- Urinalysis;

- Blood draw for PK and PD;

- ECGs, if available;

- Also all assessments included in Section 10.9.2 Telehealth Visits.

10.9.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

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

10.9.7. Efficacy Assessments

Please contact the sponsor should a participant need to use alternative measures for efficacy assessments. A plan will be devised in discussion with the sponsor and investigator.

10.9.8. Independent Oversight Committees

This is an open-label, non-randomized Phase 1 study. This study will not use a DMC.

10.10. Appendix 10: Bone Marrow Reserve in Adults

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*[12]

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head:			136.6		
	Cranium	165.8	0.75	124.3	13.1	**13.1**
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle:			86.7		
	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	**10.2**
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
VERTEBRAE	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar):			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		**1497.7**		**1045.7**	**100.0**	**100.0**

10.11. Appendix 11: RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247[13].

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to randomization and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be non-evaluable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as CR, Non-CR/Non-PD, PD, NE. Multiple non-target lesions in one organ may be recorded as a single item on the CRF (eg, ‘multiple enlarged pelvic lymph nodes’or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses might be non-evaluable.

Target Disease

1. CR: Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

2. PR: Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

3. SD: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

4. PD: 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

5. NE: Progression has not been documented, and

    - One or more target measurable lesions have not been assessed; or

    - One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or

    - One or more target lesions were excised or irradiated.

Non-target disease

6. CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

7. Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

8. PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

9. NE: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Participants requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE or Missing	No	PR
PR	Non-CR/Non-PD, NE or Missing	No	PR
SD	Non-CR/Non-PD, NE or Missing	No	Stable
NE or Missing	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of participants with only non-target disease, the following table will be used:

Objective Response Status at each Evaluation for Participants with Non-Target Disease

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
NE	No	NE
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Best Overall Response

The BOR is the best response recorded from the randomization until disease progression or death due to any cause. This is derived from the sequence of objective statuses. Objective statuses are not considered after objective progression is documented or after start of the first anticancer treatment post discontinuation of protocol treatment. BOR for each participant will be derived as one of the following categories.

- CR: At least one objective status of CR documented before progression.
- PR: At least one objective status of PR documented before progression.
- SD: At least one objective status of stable documented at least 8 weeks after randomization date and before progression but not qualifying as CR, PR.
- PD: Objective status of progression within 16 weeks of randomization, not qualifying as CR, PR or SD.
- NE: Progression not documented within 16 weeks after randomization and no other response category applies.

10.12. Appendix 12: ECOG Performance Status*[14]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

*As published in Am J Clin Oncol 5:649-655, 1982.

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. The Protocol Amendment Summary of Changes Table for past amendments can be found below:

Document	Version Date	Summary and Rationale for Changes
Amendment 1	25 Mar 2022	1.3. Schedules of Activities Table 1 and Table 2 8.4. Pharmacokinetics 9.3.3.3. Pharmacokinetic Analysis Table 8 • Corrected the visit at Day 21 to Day 22 in Cycle 1. Rationale: Correction 4.2.1. Choice of Contraception/Barrier Requirements • Added that ARV-471 is not genotoxic. Rationale: Genotoxicity study results are required for considering contraception duration based on the guideline (Guidance for Industry, Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations). 4.3.1. Dose Limiting Toxicity Definition • Added that all safety information including AEs that have occurred in the participants who were excluded from the DLT evaluation will be considered in the assessment of tolerability. Rationale: To incorporate changes requested by the PMDA following the review of the original final protocol dated 09 February 2022. Table 5. DLT Criteria

Document	Version Date	Summar and Rationale for Chan es
		• Clarified the DLT definition of Grade 3 toxicities in Non-Hematologic DLTs. • Clarified that any AE attributed to ARV-471 detected within DLT evaluation period requiring dose inte1n1ption for14 days extending beyond the end of the DLT evaluation period and to post-DLT evaluation period will also be considered a DLT. Rationale: To incorporate changes requested by the PMDA following the review of the original final protocol dated 09 Febrnaiy 2022. 5.2. Exclusion Criteria #12 • Added the breastfeeding paiiicipant (including females who ai·e cunently breastfeeding or intend to temporai·ily intenupt breastfeeding). Rationale: To incorporate changes requested by the PMDA following the review of the original final protocol dated 09 Febrnaiy 2022. 8.3.5.1. Exposme Dming Pregnancy • Updated the data collection period for details of the pregnancy from 90 days to 30 days after the last dose. Rationale: To align with the contraception period. CCI I [redacted]

Document	Version Date	Summary and Rationale for Changes
		CCI [redacted] 10.4.1. Male Paiiicipant Reproductive Inclusion Criteria 10.4.2. Female Paiiicipant Reproductive Inclusion Criteria • Updated the contrnception requirements period from at least 90 days to 30 days after the last dose of study intervention in both male and female paiiicipants. Rationale: Alignment of the criteria with the ARV-471 program level protocol 10.4.4. Contrnception Methods • Removed the ho1monal contraception methods. Rationale: Honnonal contraception methods ai·e not applicable for patients with breast cancer. In addition, other clai·ifications, administrative, and typographical modifications were made.
Original protocol	09 Feb 2022	NA

10.14. Appendix 14: Abbreviations

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

Abbreviation	Term
AE	adverse event
AI	Aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma-concentration curve
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the plasma concentration-time curve from time zero to time tau
AV	atrioventricular
BCRP	Breast Cancer Resistance Protein
BID	twice daily
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
CAP	College of American Pathologists
CBR	clinical benefit response
CDC	Centers for Disease Control and Prevention
CDK4/6	Cyclin-Dependent Kinase 4/6
CDKi	CDK4/6 inhibitors
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent clearance
C_{max}	maximum observed plasma concentration
C_{min}	lowest concentration observed during the dosing interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report

Abbreviation	Term
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
C_{trough}	pre-dose plasma concentration during multiple dosing
CV	coefficient of variation
CXDX	Cycle X Day X
CYP	cytochrome P-450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DRE	disease related events
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOT	end of treatment
ER	estrogen receptor
CCI	[redacted]
ET	endocrine therapy
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GnRH	gonadotropin-releasing hormone
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HER2	human epidermal growth factor receptor 2
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus

Abbreviation	Term
HIVAb	human immunodeficiency virus antibody
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IHC	immunohistochemistry
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
JSH	Japan Society of Hepatology
LBBB	left bundle branch block
LC-MS/MS	liquid chromatograph-tandem mass spectrometry
LFT	liver function test
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NA	not applicable
NCI	National Cancer Institute
NE	Non-evaluable
NIMP	non-investigational medicinal product
NOAEL	no-observed-adverse-effect level
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s) or progressive disease
PE	physical examination
PFS	progression-free survival
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PR	partial response
PMDA	Pharmaceuticals and Medical Devices Agency
PROTAC	PROteolysis-TArgeting Chimera
PS	performance status
PT	prothrombin time

Abbreviation	Term
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
QD	once daily
QRS	time from the beginning of the Q wave to the end of the S wave in the electrocardiogram
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QTL	quality tolerance limit
R_{ac}	accumulation ratio based on AUC (observed)
RANKL	Receptor Activator of Nuclear Factor Kappa B Ligand
RECIST	Response Evaluation Criteria in Solid Tumors
CCI	[redacted]
RP2D	recommended phase 2 dose
RP3D	recommended phase 3 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SERD	selective estrogen receptor degrader/downregulator
SERM	selective estrogen receptor modulator
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
$t_{½eff}$	effective half-life based on accumulation ratio
TBili	total bilirubin
TdP	Torsades de Pointes
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
T_{max}	time to reach maximum concentration
TME	tumor microenvironment
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VE	venous embolism
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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