Title Page

A PHASE 3, RANDOMIZED, OPEN-LABEL, MULTICENTER TRIAL OF ARV-471 (PF-07850327) VS FULVESTRANT IN PARTICIPANTS WITH ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE ADVANCED BREAST CANCER WHOSE DISEASE PROGRESSED AFTER PRIOR ENDOCRINE BASED TREATMENT FOR ADVANCED DISEASE (VERITAC-2)

Study Intervention Number:	PF-07850327
Study Intervention Name:	ARV-471 (vepdegestrant)
US IND Number:	140264
EU CT Number:	2022-500544-38-00
ClinicalTrials.gov ID:	NCT05654623
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4891001
Phase:	3
Sponsor Legal Address (Outside US):	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001 United States
Sponsor Legal Address (In US):	Arvinas Estrogen Receptor, Inc. 5 Science Park, 395 Winchester Ave. New Haven, CT 06511 United States

Brief Title: Phase 3, Open-label Study of ARV-471 (PF-07850327) vs Fulvestrant in Participants With ER(+)/ HER2(-) Advanced Breast Cancer (V**ER**ITAC-2)

Document History

Document	Version Date
Amendment 3	6 November 2024
Amendment 2	24 May 2023
Amendment 1	25 October 2022
Original protocol	15 June 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 3 (6 November 2024)

Overall Rationale for the Amendment: The protocol is amended to address health authority feedback on statistical analyses due to emerging evidence of differential efficacy of SERDs in ESR1 mutation positive versus ESR1 mutation negative patients.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Change statistical hypothesis testing strategy from truncated Hochberg procedure to graphical multiple testing strategy.	Statistical hypothesis testing strategy was amended upon FDA recommendation based on emerging evidence of differential efficacy of SERDs in ESR1 mutation positive vs ESR1 mutation negative patients. The new hypothesis testing strategy incorporates a testing order based on clinical importance and logical relevance per FDA comments.	Section 1.1 Synopsis Section 4.1 Overall design Section 9.1 Statistical hypotheses Section 9.1.2 Multiplicity Adjustment Section 9.4 Interim analysis Section 9.5 Sample size determination
Pre-specify a minimum efficacy effect in PFS for ESR1 mutation negative	To address FDA request and to pre-specify a minimum efficacy effect in	Section 9.1 Statistical hypotheses

Description of Change	Brief Rationale	Section # and Name
subgroup according to Rothmann criteria.	ESR1 mutation negative patients for benefit/risk evaluation.	
Non-substantial Modification(s)		
Potential for pausing enrollment of one population (either ESR1 mutation or wild type participant) has been removed.	An enrollment pause was never implemented as no meaningful imbalance was observed. Thus, text regarding a potential pause was removed.	Section 1.3 Schedule of Activities Table 1 and Section 4.1 Overall Design
Enrollment will continue until approximately 280 participants with the ESR1 mutation have been enrolled.	The number of ESR1 mutant participants is needed to ensure number of events for planned statistical analysis	Section 1.1 Synopsis and Section 4.1 Overall Design
Updated regulatory information in Section 2.2.4 based on the elacestrant approval in 2023.	Elacestrant has been registered in 2023 and fulvestrant is no longer the only approved SERD.	Section 2.2.4 SERD
Development and reproductive toxicity have been added as an additional potential risk of clinical significance	Section revised in alignment with the IB dated Oct 2024. The change is considered non-substantial since risk mitigation already in place based on ARV-471 mechanism of action.	Section 2.3.1 Risk Assessment
Text updated to include the 3 months formulation to the already specified 28 days formulation.	In addition to the LHRH formulation given every 28 days, the use of the 3 months formulation is acceptable. This	Section 6.9.1. Luteinizing Hormone-Releasing Hormone Agonist and Section 1.3. Schedule of Activities Table 2

Description of Change	Brief Rationale	Section # and Name
This change incorporates the Protocol Administrative Change Letter (PACL) dated 06-Jul-2023.	formulation will reduce participants' burden without compromising the LHRH efficacy.	
Following text added in the SOA notes: PROs mandatory unless the electronic devices will never be available due to local restrictions. In this case completion of any PRO version including the paper version is not required. This change incorporates the PACL dated 06-Jul-2023.	Clarified that the PRO questionnaires (EuroQol EQ5D-5L, EORTC QLQ-C30; EORTC QLQ-BR23, BPI-SF, Evening Daily Diary, Patient Preference Questionnaire) are required assessments unless the electronic devices cannot be imported into the country. In these cases, the collection of the PRO data is not required. Importation of the electronic PRO (ePRO) devices in certain countries (eg, Turkey) are impacted due to recent updates to local/government regulations. In addition, the ePRO vendor does not currently have local resources for in-country device provisioning. Despite availability of paper PROs, the completion of only this paper version for the duration of study participation is not a valid option due to the high probability of missing data, which will impact the overall completion rate and may jeopardize data interpretation. Participants	Section 1.3 Schedule of Activities Table 2

Description of Change	Brief Rationale	Section # and Name
	who do not complete any PRO will be treated as non-participants rather than non-completers and therefore will not impact the study's PRO completion.	
Text updated to extend the collection time window for electrolyte testing. This change incorporates the PACL dated 06-Jul-2023.	The collection time window for the electrolyte testing has been extended until –2 days prior to dosing to be consistent with the other laboratory safety tests. This change does not impact patient's safety. The ECG will be performed on Day 1 of the cycles (as per Table 3). If electrolyte testing is not performed on Day 1 of the cycle (i.e. performed up to -2 days), electrolytes test must be repeated on Day 1 only in case of ECG abnormalities. This is consistent with Section 6.6.2.3. of the study protocol, that requires the evaluation and correction of possible alternative reversible causes such as serum electrolytes abnormalities in the event of QTc prolongation.	Section 8.3.3 Electrocardiograms and Section 1.3 Schedule of Activities Table 2 & Table 3
The PK samples should be collected within 2.5 hours prior to dosing (not 2 hours) for consistency	Transcription error corrected.	Section 1.3 Schedule of Activities Table 3

Description of Change	Brief Rationale	Section # and Name
with the same information reported in this Table 3. This change incorporates the PACL dated 06-Jul-2023.		
Instructions for ARV-471 administration have been updated to clarify that the morning intake is not a mandatory requirement. This change incorporates the PACL dated 21-Sep-2023.	ARV-471 drug intake is recommended at approximately the same time in the morning. However, no issues from a safety perspective have been identified in case the drug is taken later in the same day.	Section 1.3 Schedule of Activities Table 2, Section 5.3.2. Meals and Dietary Restrictions and Section 6.1.1.1 ARV-471
Footnote added to allow up to 4 hours pre-dose time window for evaluation assessment reported in Table 3. This change incorporates the PACL dated 21-Sep-2023.	The time window of 2.5 hours pre-dose may be extended up to 4 hours to accommodate site needs as long as all samples are collected on each evaluation day as per Schedule of Activities.	Section 1.3 Schedule of Activities Table 3
Inclusion criterion 3b updated to clarify that HER-2 status for inclusion should be assessed on the same tumor sample used for characterizing the ER status (on the most recent tumor biopsy). This change incorporates the PACL dated 21-Sep-2023.	Text added for clarification purposes.	Section 1.1 Synopsis and Section 5.1 Inclusion Criteria
Faslodex® included.	Text was added to clarify that Faslodex® may also	Section 6.1 Study Intervention(s) Administered

Description of Change	Brief Rationale	Section # and Name
This change incorporates the PACL dated 21-Sep-2023.	be used in addition to generic Fulvestrant.	
Text updated to include the instruction to consult the respective local product label of the P-gp substrate before use and to allow the use of H2 receptor antagonists or antacids when ARV-471 is taken with a moderate-fat meal (400-800 calories, approximately 35% fat). This change incorporates the PACL dated 21-Sep-2023.	The updates to the text provide additional clarification on administration of P-gp substrates and H2 receptor antagonists and antacids that were included in the IB dated August 2023 to ensure consistency across documents. For P-gp substrates, details were added to refer to the respective product labels. Administration requirements around H2 receptor antagonists or antacids were loosened due to emerging data.	Section 6.9.4 Concomitant Treatments to be used with caution or not recommended
Text updated in Inclusion Criteria 3a, 3d to clarify that for those study participants where a de novo biopsy is clinically contraindicated an archival tumor tissue at initial diagnosis is acceptable. This change incorporates the PACL dated 25-Jan-2024.	The collection of a de novo biopsy may impact the participant's safety if clinically contraindicated.	Section 1.1 Synopsis, Section 5.1 Inclusion Criteria & Section 8.7.1 Tumor Biopsies
Text added to clarify that results of cholesterol and triglycerides are not needed for retreatment.	This change does not impact participant's safety and allows more flexibility for sites.	Section 1.3 Schedule of Activities Table 2

Description of Change	Brief Rationale	Section # and Name
This change incorporates the PACL dated 25-Jan-2024.		
The "Medical Device Constituent Supplemental Form" has been removed. This change incorporates the PACL dated 25-Jan-2024.	If an SAE occurs in the setting of a medical device deficiency, the SAE must be recorded using the Clinical Trial (CT) SAE Report Form or Pfizer SAE Submission Assistant (PSSA) tool. The Medical Device Constituent Supplemental Form is no longer a valid option to report a medical device deficiency and should not be chosen.	Section 8.4.9.3. Prompt Reporting of Device Deficiencies
The process for contacting a medically qualified individual has been changed. This change incorporates the PACL dated 25-Jan-2024.	The process for contacting a medically qualified individual has changed from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a Study Team Contact List. The Emergency Contact Card is being replaced by a study information card and will no longer be referenced.	Section 10.1.12 Appendix 1 Sponsor's Medically Qualified Individual and Section 10.16. Appendix 16: Abbreviations
Text added to clarify that if participants will be contacted for survival information the investigators may ask also information on poststudy anticancer therapies, as already specify in the sentence above.	Typo. Text added to align with previous sentence in the same paragraph	Section 7.1.1.2 Survival Follow-up

Description of Change	Brief Rationale	Section # and Name
Text added for the latest EU-CTR.	Text added to comply with latest EU-CTR requirements.	Section 10.11 Appendix 11 Country Specific Requirements

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Open-Label, Multicenter Trial of ARV-471 (PF-07850327) vs Fulvestrant in Participants with Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer Whose Disease Progressed After Prior Endocrine Based Treatment for Advanced Disease (V**ER**ITAC-2)

Brief Title: Phase 3, Open-label Study of ARV-471 (PF-07850327**)** vs Fulvestrant in Participants With ER(+)/ HER2(-) Advanced Breast Cancer (V**ER**ITAC-2)

Regulatory Agency Identification Number(s):

US IND Number:	140264
EU CT Number:	2022-500544-38-00
ClinicalTrials.gov ID:	NCT05654623
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4891001
Phase:	3

Rationale:

In nonclinical studies, ARV-471 has demonstrated robust estrogen receptor (ER) degradation, superior activity against clinically relevant ER mutated forms (eg, Y537S and D538G), and improved tumor growth inhibition (TGI) as single agent compared to fulvestrant in ER wild type and estrogen receptor 1 (ESR1) mutant patient-derived xenograft models. In the first in human (FIH) study, ARV-471 administered orally once daily (QD) as a single agent appears to be safe and well tolerated across total daily doses of 30 mg to 700 mg with preliminary evidence of efficacy in participants pretreated with cyclin dependent kinase 4/6 (CDK4/6) inhibitor plus endocrine therapy. These results support the hypothesis that ARV-471 may represent an important therapeutic approach in patients with ER(+)/human epidermal growth factor receptor 2 negative [HER2(-)] advanced breast disease.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To demonstrate that ARV-471 is superior to fulvestrant in prolonging progression-free survival (PFS) by blinded independent central review (BICR) assessment in	• PFS, defined as the time from the date of randomization to the date of first documented disease progression, as determined by BICR assessment per Response Evaluation Criteria in Solid	• The primary estimand is to compare the treatment effect (as measured by hazard ratio [HR]) of ARV-471 versus fulvestrant on PFS in participants with ER(+)/HER2(-) aBC (all participants and participants with ESR1 mutation-

Objectives	Endpoints	Estimands
participants with ER(+)/HER2(-) advanced breast cancer (aBC) (all participants and participants with ESR1 mutation-positive breast cancer [BC]) who have received prior endocrine-based treatment for their advanced disease	Tumors Version 1.1(RECIST v1.1), or death due to any cause, whichever occurs first	positive BC) who have received prior endocrine-based treatment for their advanced disease. PFS will be analyzed using the stratified log-rank test and Kaplan-Meier method. PFS data will be censored for those who did not have a PFS event, discontinued the study treatment due to withdrawal of consent prior to an event, started a new anti-cancer therapy prior to an event, had an event after an unacceptably long interval, or lost to follow-up.
Key Secondary:	**Key Secondary:**	**Key Secondary:**
• To demonstrate that ARV-471 is superior to fulvestrant in prolonging overall survival (all participants and participants with ESR1 mutation-positive BC)	• Overall Survival (OS), defined as the time from the date of randomization to the date of death due to any cause	• The estimand for OS is to compare the treatment effect (as measured by HR) of ARV-471 versus fulvestrant in participants with ER(+)/HER2(-) aBC (all participants and participants with ESR1 mutation-positive BC) who have received prior endocrine-based treatment for their advanced disease. OS will be analyzed using the stratified log-rank test and Kaplan-Meier method. OS data will be censored for those who did not have an OS event.
Secondary:	**Secondary:**	**Secondary:**
• To compare measures of tumor control between treatment arms and to evaluate the duration of response (DOR) by BICR assessment within each treatment arm	• Objective Response (OR): confirmed complete response (CR) or partial response (PR) by BICR assessment • Clinical benefit response (CBR) defined as confirmed CR or PR at any time or stable disease (SD) or non-CR/non-progressive disease (PD) ≥24 weeks by BICR assessment • DOR by BICR assessment	• Not applicable.
• To evaluate safety and tolerability between the treatment arms	• Type, incidence, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), seriousness and relationship to study medications of adverse events (AEs) and any laboratory and electrocardiogram (ECG) abnormalities	• Not applicable.
• To characterize the effects of ARV-471 on corrected QT interval (QTc)	• QTc	• Not applicable.
• To evaluate patient reported outcomes between two treatment arms	• European Organization for the Research and Treatment of Cancer and Quality of Life Questionnaire (EORTC QLQ-C30)	• Not applicable.

Objectives	Endpoints	Estimands
	• European Organization for the Research and Treatment of Cancer and Quality of Life Questionnaire-Breast Cancer specific (EORTC QLQ-BR23) • European quality of life five-dimension five-level scale (EuroQol; EQ-5D-5L) • Brief pain inventory short form (BPI-SF)	
• To determine plasma concentrations of ARV-471 and ARV-473 after repeated dosing of ARV-471	• Plasma concentrations of ARV-471 and its epimer ARV-473	• Not applicable.
• To assess changes from baseline levels in plasma circulating tumor DNA (ctDNA)	• ctDNA plasma quantitative changes from baseline to evaluate their associations with clinical outcomes	• Not applicable.

Overall Design:

This is an international Phase 3 multicenter, randomized, open-label, parallel-group study aimed to demonstrate that ARV-471 is superior to fulvestrant in prolonging the PFS (by BICR assessment) in participants with ER(+)/HER2(-) aBC who have progressed after prior endocrine treatment-based regimen(s) for advanced disease.

Approximately 560 participants (of which approximately 280 are participants with ESR1 mutation) will be randomly assigned to Arm A (ARV-471, PF-07850327) or Arm B (fulvestrant). Enrollment will continue until approximately 280 participants with the ESR1 mutation have been enrolled.

Participants will be randomly assigned on a 1:1 basis to:

- Arm A: (Investigational Arm; n ≈ 280). Participants will receive ARV-471 200 mg orally, once daily on a 28-day continuous dosing schedule.
- Arm B: (Comparator Arm; n ≈ 280). Participants will receive fulvestrant 500 mg, intramuscularly on Days 1 and 15 of Cycle 1 and then on Day 1 of each cycle starting from C2D1 (28-day cycle).

Participants will be stratified by ESR1 mutational status (Mutant, Yes/No) and visceral disease (Yes/No).
Visceral refers to lung, liver, brain, pleural, and peritoneal involvement.

Pre- and peri-menopausal female and male participants must receive therapy with an LHRH agonist starting on Cycle 1 Day 1 (if not already on treatment) and continued during the study.

Crossover between treatment arms will NOT be allowed.

The study includes a QTc sub-study in approximately 80 participants in Arm A enrolled at selected sites which will evaluate the effect of ARV-471 on QTc interval via triplicate ECGs (central reading) time-matched with PK draws.

Evaluation of ESR1 status (wild-type versus ESR1 mutated) will be performed using ctDNA blood samples. ctDNA blood samples may be used for development of companion diagnostics.

Safety will be monitored at regular intervals (once per cycle) throughout the study by laboratory tests, triplicate ECGs (first 3 cycles and at the end of treatment [EOT]) and clinical visits. Blood samples for pharmacokinetics analysis of ARV-471 and its epimer, ARV-473 will be collected up to Cycle 7 in Arm A participants.

Participants will undergo regular efficacy assessments by computed tomography (CT)/ magnetic resonance imaging (MRI) scan (ie, every 8 weeks for the first 48 weeks from date of randomization and then every 12 weeks thereafter) and bone scan, if applicable (ie, every 24 weeks from randomization date). Efficacy analyses will be performed using BICR tumor assessments as the primary data source. All radiographic images, as well as other information collected on-study will be verified by BICR to determine the protocol defined endpoints of disease response and progression.

PRO assessments will be administered by various questionnaires to evaluate the impact on quality of life, functioning, symptoms, general health status, and preference of route administration in both Arms. Worst pain severity, pain interference, pain medication usage (in both Arms) and injection site pain (only in Arm B) will be evaluated and captured in the evening daily diary.

Serial ctDNA blood will be collected to assess ctDNA plasma quantitative change. Moreover, the association between breast tumor genomic alterations and tumor sensitivity/resistance to ARV-471 will be assessed in serial ctDNA blood and tumor samples. A blood sample for DNA extraction (ie, Retained Research Sample for Genetics) will be collected, unless prohibited by local regulations, or by Institutional Review Boards (IRBs)/ ethics committees (ECs) for research related to the study intervention(s) and advanced breast cancer.

The screening period should occur within 28 days prior to randomization. Study intervention will be administered in 28-day cycles. Participants will continue to receive assigned study intervention until one of the following reasons occurs:

- Objective disease progression assessed by Investigator; however, participants with disease progression as per RECIST v1.1 who are continuing to derive clinical benefit from the study intervention (ie, positive benefit/risk assessment as assessed by investigator), will be eligible to continue study intervention;
- 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.

An external data monitoring committee (E-DMC) will be established to review aggregate safety data to monitor safety and tolerability by treatment arm.

A Global Steering Committee will be established at the program level for ARV-471. It will be responsible for providing scientific advice and medical input on the ongoing and future clinical development plans for ARV-471 in ER(+) breast cancer, including for this study.

It is anticipated that the final PFS analysis will occur at approximately 310 PFS events in all participants population and approximately 165 PFS events in the ESR1 *mutant* subgroup population. The final OS analysis will occur at approximately 396 OS events in all participants population and 194 OS events in ESR1 *mutant* subgroup population.

Number of Participants:

Approximately 560 participants will be randomized in the study.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

- Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening.

    a. Female participants under 60 years of age, with cessation of regular menses for 12 consecutive months and with no alternative medical cause, must have a follicle-stimulating hormone (FSH) level within the post-menopausal level, as per local laboratory reference range.

    b. Pre/peri-menopausal female and male participants must agree to initiate or continue to use an luteinizing hormone-releasing hormone (LHRH) agonist.

    c. Woman/women of childbearing potential (WOCBP) female and male participants must agree to use contraception.

- Histological or cytological confirmation of breast cancer with evidence of locoregional recurrent or metastatic disease which is not amenable to surgical resection or radiation therapy with curative intent.
    a. Documented ER(+) tumor, defined as ER(+) ≥10% stained cells by an assay consistent with local standards, on the most recent tumor biopsy, ie, at diagnosis of recurrence or metastatic disease. The sole exception is those participants with bone only disease and participants in whom the collection of a biopsy is clinically contraindicated, for whom ER(+) using archival tissue at initial diagnosis is acceptable.

    b. Documented HER2(-) tumor by either immunohistochemistry (IHC) or *in-situ* hybridization per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines on the most recent tumor biopsy and as per above in inclusion criterion a.

    c. Participants who have bilateral breast cancers which are <u>both</u> ER(+)/HER2(-) are eligible.

    d. Participants must provide a blood sample AND a tumor sample collected at the time of diagnosis of locoregional recurrent or metastatic disease. If not available, a de novo biopsy is required, unless the participant has bone only disease or in whom the collection of a biopsy is clinically contraindicated. In these cases, an archival tumor tissue at initial diagnosis is acceptable.

- Prior therapies for locoregional recurrent or metastatic disease must fulfill all the following criteria:
  Note: Progression during or within 12 months from the end of adjuvant therapy is counted as a line of therapy in advanced/metastatic setting.

  a. One line of CDK4/6 inhibitor therapy in combination with endocrine therapy (ET). Only one line of CDK4/6 inhibitor is allowed in any setting.

  b. ≤ 1 endocrine therapy in addition to CDK4/6 inhibitor with ET.

  c. Most recent endocrine treatment duration must have been given for ≥6 months prior to disease progression. This may be the endocrine treatment component of the CDK4/6 inhibitor line of therapy.

  d. Radiological progression during or after the last line of therapy.

- At least one measurable lesion as defined by RECIST version 1.1. Bone only disease: participants with only non-measurable disease are eligible.

- ECOG PS ≤1

Exclusion Criteria

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

- History of any other solid tumor malignancies within the past three years, except for the following: (1) adequately treated basal or squamous cell carcinoma of the skin; (2) curatively treated in situ carcinoma of the cervix. For all other solid tumors, must have been curatively treated and with no evidence of disease for >3 years. Participants with inflammatory breast cancer are excluded.

- Participants with newly diagnosed brain metastasis or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Participants with a history of CNS metastases or cord compression are eligible if they have been definitively treated (e.g., radiotherapy, stereotactic surgery) and clinically stable (including participants with residual CNS symptoms/deficits) off enzyme-inducing anticonvulsants and steroids for at least 14 days prior to randomization.

- Participants in visceral crisis at risk of immediately life-threatening complications in the short term, including participants with massive uncontrolled effusions (pleural, pericardial, and peritoneal), pulmonary lymphangitis, or liver involvement >50%.

- Impaired cardiovascular function or clinically significant cardiovascular diseases.

- Prior treatment with:
    a. ARV-471, fulvestrant, elacestrant, mammalian target of rapamycin (mTOR), phosphoinositide-3-kinase (PI3K), protein kinase B (AKT) pathway inhibitors, poly adenosine diphosphate-ribose polymerase (PARP) inhibitor, other investigational agents (including novel endocrine therapy, any selective estrogen receptor degraders [SERDs], selective estrogen receptor covalent antagonists [SERCAs], complete estrogen receptor antagonists [CERANs]) for any setting.
    b. prior chemotherapy for advanced/metastatic disease.

  Participation in other studies involving investigational drug(s) within 28 days prior to randomization. If in the follow-up (FU) Phase, the participant is eligible provided at least 5 half-lives have elapsed from the last dose.

- Inadequate liver, kidney and bone marrow function.

Study Arms and Duration:

Study Intervention		
Intervention Name	ARV-471 (PF-07850327)	Fulvestrant
Arm Name (group of participants receiving a specific treatment or no treatment)	A (Investigational)	B (Comparator)
Dose Formulation	Tablet	Solution for intramuscular (IM) injection
Unit Dose Strength(s)	100 mg	250 mg/5 mL
Route of Administration	Oral	IM
Use	Experimental	Active comparator
Investigational medicinal product (IMP) or non-investigational medicinal product/auxiliary medicinal products (NIMP/AxMP)	IMP	IMP

Study Arm(s)		
Arm Title	Arm A (ARV-471)	Arm B (Fulvestrant)
Arm Type	Experimental	Active comparator
Arm Description	Participants will receive two ARV-471 100 mg tablets (200 mg QD) administered orally, once daily, on Days 1-28 of each 28-day cycle.	Participants will receive fulvestrant as two 5 mL IM injections (250 mg/5 mL) on Days 1 and 15 of Cycle 1 and then on Day 1 of each cycle starting from C2D1 (28-day cycle).

Statistical Methods:

The primary endpoint is PFS assessed by BICR, which is defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) per RECIST v1.1, or death due to any cause, whichever occurs first.

The key secondary endpoint is OS, which is defined as the time from date of randomization to date of death due to any cause.

The study will perform statistical hypotheses tests in each of the two populations: 1) all randomized participants, and 2) participants with ESR1 mutation.

Primary endpoint family:

$H_{0\ \text{all participants}}$: $HR_{PFS} \geq 1$ vs $H_{1\ \text{all participants}}$: $HR_{PFS} < 1$

$H_{0\ \text{ESR1 }\textit{mutant}\text{ participants}}$: $HR_{PFS} \geq 1$ vs $H_{1\ \text{ESR1 }\textit{mutant}\text{ participants}}$: $HR_{PFS} < 1$

where HR_{PFS} is the hazard ratio (ARV-471 vs fulvestrant) of PFS.

And secondary endpoint family:

$H_{0\ \text{all participants}}$: $HR_{OS} \geq 1$ vs $H_{1\ \text{all participants}}$: $HR_{OS} < 1$

$H_{0\ \text{ESR1 }\textit{mutant}\text{ participants}}$: $HR_{OS} \geq 1$ vs $H_{1\ \text{ESR1 }\textit{mutant}\text{ participants}}$: $HR_{OS} < 1$

where HR_{OS} is the hazard ratio (ARV-471 vs fulvestrant) of OS.

A graphical multiple testing strategy will be used for PFS and OS testing to maintain the overall 1-sided type I error rate within 2.5% (α) at the whole study level.

No interim analysis is planned for the primary endpoint PFS.

Two interim analyses for efficacy are planned for the key secondary endpoint of OS. The first OS interim analysis will be performed at the time of the final PFS analysis. The second OS interim analysis will be performed at 130 OS events in participants with ESR1 mutation and 265 OS events in all participants population (approximately 67% of total OS events required for final analysis).

For PFS in the all participants population, based on a 1:1 randomization allocation ratio, a total of 310 PFS events will provide 92.5% power for a 1-sided log-rank test at a 0.01875 significance level to detect a hazard ratio [HR] < 0.67. For PFS in participants with ESR1 mutation, a total of 165 PFS events will provide 88% power for a 1-sided log-rank test at a 0.01875 significance level to detect a hazard ratio [HR] < 0.60.

It is estimated that approximately 560 participants will be needed to observe the 310 PFS events in all participants population, and out of which, approximately 280 participants with ESR1 mutation are required to observe 165 PFS events in the subgroup population.

All efficacy analyses will be performed using the full analysis set (FAS), defined as all participants who were randomized to the study treatment. Efficacy analyses (PFS, objective response rate [ORR], DOR, CBR) will be performed using a BICR assessment as the primary data source.

All safety analyses will be performed on the safety analysis set (SAS), defined as all randomized participants who receive at least 1 dose of study intervention. Severity of the AEs will be graded according to the NCI CTCAE v5.0.

Ethical Considerations:

In non-clinical studies, ARV-471 as a single agent demonstrated *in vitro* potent and robust ER degradation even in the presence of clinically relevant, mutated forms of ESR1.

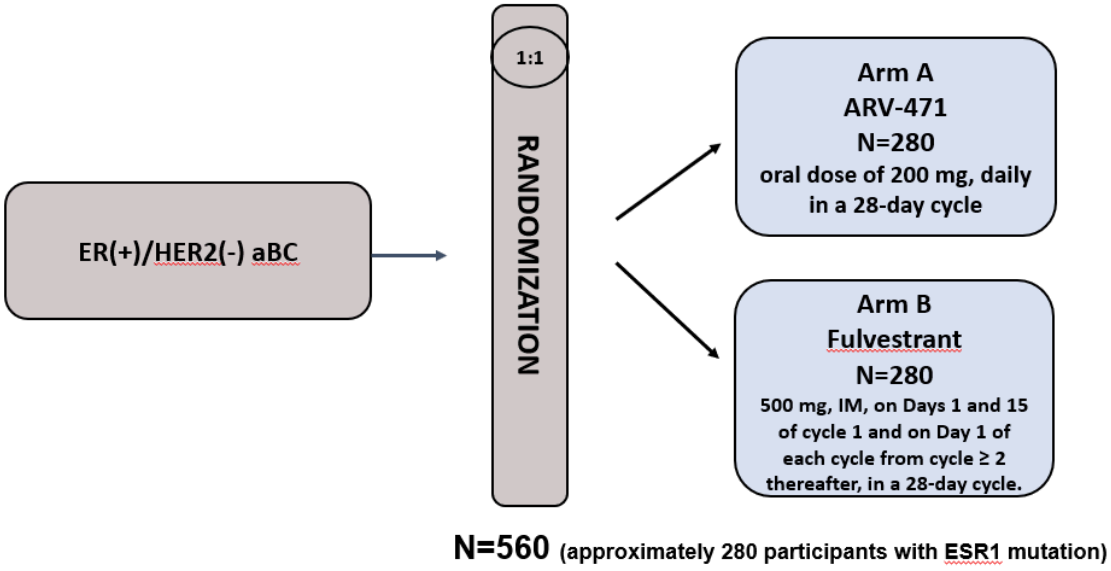
Initial safety data reported from participants treated with ARV-471 monotherapy across multiple doses in the ARV-471-mBC-101 FIH study (Part A dose escalation of ARV-471 of total daily doses of 30 to 700 mg QD and Part B dose expansion of ARV-471 at 200 mg QD and 500 mg QD, N=149) showed ARV-471 was well tolerated, without any dose limiting toxicities. Most treatment-related adverse events were Grade 1 or Grade 2 in severity. Data from the monotherapy dose escalation and dose expansion at ARV-471 200 mg QD and 500 mg QD support the monotherapy dose selection of ARV-471 200 mg QD as RP3D, based on the lack of clear differences in efficacy (by CBR) and no meaningful differences in the overall safety between ARV-471 200 mg QD and 500 mg QD, except for an apparent higher risk of potential QTc prolongation and dose reductions observed at ARV-471 500 mg QD monotherapy dose. Promising preliminary efficacy by CBR and ORR was observed for all ARV-471 doses.

Participants may experience improvements during the study and will benefit from more intense monitoring and assessments compared to usual standard of care. The number of visits or other tests/assessments will only slightly exceed what is usually required with routine standard of care and should not create a significant risk to participant health. The minimum number/volume of blood samples and of visits/all other tests requested are designed to reduce participant's burden without compromising the safety/efficacy evaluations and investigational purposes.

Overall, preliminary data from the ongoing FIH ARV-471-mBC-101 study suggest that ARV-471 may represent an important therapeutic option in participants with ER(+)/HER2(-) aBC who have progressed after prior endocrine-based treatment(s) for their advanced disease.

Given current data the anticipated benefits that may be afforded to participants with ER(+)/HER2(-) advanced breast cancer outweigh the potential risks identified in association with ARV-471.

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 procedure and assessment required for compliance with the protocol.

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

Table 1. SoA: Prescreening

The purpose of the prescreening visit is to obtain blood samples to evaluate the potential participant's estrogen receptor gene (ESR1) status (wild-type or mutated). Screening activities may be performed while waiting for ESR1 test results/approval of prior ESR1 status, but ESR1 status must be available before randomization. The sponsor will monitor the frequency of the ESR1 status (wild-type or mutated) across the study population (see Section 9.5) to evaluate the proportion of wild-type or mutated ESR1 status (targeting approximately 280 participants with wild type ESR1/280 participants with mutated ESR1).		
General Activities	**Prescreening**	**Comments**
		Timing from signing pre-screening consent to randomization should not exceed 6 weeks. If combining prescreening and screening, screening procedures should be completed within 28 days from main consent of the study to randomization unless otherwise specified.
Prescreening Informed Consent, SSID Number	X	Prescreening ICD must be signed before any prescreening activity is performed as per below: - blood sample collection for ESR1 status evaluation - ask for sponsor approval (with the exception of participants in China) for using a prior ESR1 status result. Sponsor approval may be obtained if the following criteria are met: - The test result confirms ESR1 mutated status (will not be accepted for wild-type status results) - Result is provided using an FDA approved test using ctDNA/tumor sample - Participant's ctDNA sample/tumor sample was collected within 6 months from randomization in the current study.

Table 1. SoA: Prescreening

ctDNA Blood Sample	X	Mandatory: Three samples of 10 mL each of whole blood (only two samples of 10 mL blood sample for China) must be collected. Samples to be collected: • For all participants with the exception of China: The collection of the 3 samples is mandatory and will be used either for ESR1 status evaluation or for retrospective ESR1 confirmation after participants' randomization (only for the participants with an acceptable and approved prior ESR1 status result) and may also be used for the development of companion diagnostics. One of the 3 samples is to be processed into plasma at the study site as per Lab manual instructions. The other two whole blood samples will be sent directly to the laboratory identified for analysis. See Section 8.1.1 and Laboratory Manual. • For participants in China: Two samples are mandatory for ESR1 status evaluation: the remaining sample may be also used for development of companion diagnostics. The sample may be also used for tumor molecular profile/ctDNA level and ctDNA burden if the participants are randomized in the trial. See Section 8.1.1 and Laboratory Manual. ESR1 test will be performed using a NGS test that evaluates other genes in addition to ESR1 gene. The results of the other genes will not be collected in the CRF.
Demography	X	
Disease Characteristics	X	See Section 8.1.1
AE Collection/Review	X	Record study procedure-related AEs in the eCRF from the time blood sample collection is performed through and including 14 days or longer in case of serious complications (see Appendix 3 for AE/SAE).

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Clinical Assessments								
Registration and Informed Consent Process	X							• ICD must be obtained within 28 days of randomization and prior to any protocol required assessments being performed unless otherwise specified eg, assessments by imaging • See Appendix 1 and Section 10.1.3
Screen for Inclusion/Exclusion Criteria	X							• See Section 5.1 and Section 5.2
Physical Examination* /Vital signs*	X	X	X	X	X			• C1D1 PE not required if acceptable screening assessment is performed within 7 days from randomization Height at screening only and weight at screening, at each cycle and at the EOT. • See Section 8.3.1 and Section 8.3.2

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere. d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1). e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Medical/ Oncological History	X							• See Section 8.1.2
ECOG PS	X							• Participants must have an ECOG PS ≤1 as per IC Number 6. • See Section 5.1, and Appendix 14
12-Lead ECG*	See Table 3							

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
LHRH agonist*		X (Every 28 days/3 months from Cycle 1 Day 1)					X (at PI discretion)	• Pre/peri-menopausal female and male participants must start LHRH agonist on Cycle 1 Day 1 (if not already on treatment) and continue throughout the active treatment phase every 28 days/3 months (depending on the LHRH formulation) irrespective of cycle duration and until 28 days after the last dose. • Participants already on treatment with a 28 days/3-month LHRH formulation can continue it. • LHRH agonist during the survival FU should be given at the PI's discretion in both arms. • If LHRH agonist is administered at home, the administration details will be collected in a dosing diary. • See Section 6.9.1.

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere. d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1). e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Contraception Compliance check (as applicable)*	X	X	X	X	X	X (up to 30 days)		• WOCBP and male participants: contraception is mandatory Regular checks are required at times noted in this table. • See Appendix 4 for details on contraception requirements and guidance.
Laboratory Studies-								
Hematology*	X	X	X	X	X	X (Only if laboratory abnormalities not resolved at EOT)		• C1D1 assessment not required if acceptable screening assessment is performed within 7 days prior to randomization. • Refer to Section 8.3.4 and Appendix 2

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Blood Chemistry*	X	X	X	X	X	X (Only if laboratory abnormalities not resolved at EOT)		• C1D1 assessment not required if acceptable screening assessment is performed within 7 days prior to randomization with the exception of electrolytes (sodium, potassium, magnesium, total calcium) that should be assessed on C1D1 (with a time window of -2 days, see Table 3. Assessments must be performed at each visit with the exception of: • **Glucose (fasting) and HbA1C (fasting)** only required at screening, C1D1 and then every 3 cycles (eg, Cycles 4, 7, 10 etc.) and during the first 2 years of study treatment (until Cycle 25) from randomization and EOT • Cholesterol and triglycerides required at screening, C4D1, C7D1 and then every 6 cycles and at the EOT. Results of these tests are not needed for retreatment. • Total Calcium and magnesium are performed at screening, C1D1, C2D1, C3D1 and EOT. • Refer to Section 8.3.4 and Appendix 2

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
HBV, HCV and HIV Tests	[X]							• Only if required by local regulations.
Coagulation	X							• See Section 8.3.4 and Appendix 2
FSH (as applicable)	X							• To confirm a postmenopausal status of female participants under 60 years of age, cessation of regular menses for 12 consecutive months and with no alternative medical cause. • See Appendix 2 and Appendix 4 .
Pregnancy Test (as applicable)*	X	X	X	X	X	X		• For WOCBP only. A serum pregnancy test is mandatory at screening. • Post screening, pregnancy tests (urine or serum tests with a sensitivity of at least 25 mIU/mL) are required. • Additional pregnancy tests may be performed at any time as per Investigator judgment or if required by local regulations or IRBs/ECs. • See Section 8.3.5, Appendix 2.

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Disease Assessments								
Tumor assessments (other than Bone scan)	X	◄--► Every 8 weeks (±7 days) for the first 48 weeks from the date of randomization. Then every 12 weeks (± 7 days) thereafter from the date of randomization			X			• Images, as well as all the other information as per Section 8.2.1.2 must be sent for central reading on an ongoing basis (as soon as they are available) and until PD is confirmed by BICR regardless of the initiation of a new anticancer therapy. • Tumor assessments should continue as per Section 8.2.1 and Section 8.2.1.2. • On active treatment phase bone scan should be performed only if needed as per Section 8.2.1 requirement. • See Section 8.2.1.1 for further details on treatment continuation beyond progression. • Please see Section 8.2.1 for CR/PR confirmation. • Post-Treatment oncologic assessments (including bone scan, if applicable) are required only for participants who discontinued the study treatment for reason other than PD. • See Section 8.2
Radionuclide Bone Scan, Whole Body	X	◄--► Every 24 weeks (± 7 days) from the date of randomization			X			

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Randomization and Study Treatment								
Randomization	X							• Randomization must occur after having carefully reviewed all eligibility criteria and confirmed they are satisfied. • At randomization, randomization number and treatment arm are assigned. • Study treatment must start within 3 days after randomization. • See Section 6.3
ARV-471 (Arm A)*		Once Daily ◄--►						• ARV-471 is given orally, in continuous daily dosing, for a 28-day cycle, with food at approximately the same time preferably in the morning. • See Section 6.1.1 and Section 6.1.1.1 for details on drug intake.
Fulvestrant (Arm B)*		X (Days **1** and **15**)	X	X				• Fulvestrant should be administered intramuscularly on Days **1** and **15** (±2) of Cycle 1. Then from Cycle ≥2, on **Day 1** of each cycle. • Refer to Section 6.1.1.2

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Other Clinical Assessments								
Drug Compliance*		◄--►						• Any unused tablets of ARV-471 must be returned to the clinic for drug accountability. • From Cycle 2 onward, compliance will be performed at each cycle, prior to dispensing drug for the following cycle. • A dosing diary for ARV-471 will be given to participants to record dosing compliance • Refer to Section 6.2 and Section 6.5
Adverse Event Reporting*	X	X	X	X	X	X		• See Section 8.4.1, Section 8.4.9, Appendix 3, and Appendix 9 for details on AE/SAE reporting requirements during the active reporting period and for SAE reporting requirements after the end of reporting period.
Concomitant Medications/ Treatments*	X	X	X	X	X	X		• See Section 6.9 and Appendix 10

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
PRO Assessments*: • EuroQol; EQ-5D-5L; • EORTC QLQ-C30; • EORTC QLQ-BR23 • BPI-SF	X	X	X	X (Cycles 3, 4, 5, 6 and then every other Cycle, ie, cycles 8, 10, 12, etc)	X	X		• All self-assessment questionnaires should be completed by the participants prior to any Day 1 procedure. • See Section 8.9, Appendix 14 • Female and male versions of the EORTC QLQ-BR23 questionnaire will be utilized depending on the participant's gender. • Questionnaire by paper or electronic. If both versions are available, electronic version must be completed. • PROs mandatory unless the electronic devices are not available due to local restrictions. In this case completion of any PRO version including the33 paper version is not required.
PRO/ Evening Daily Diary: • mBPI-SF • pain medication		Daily						• "Evening daily diary" to be filled in the evening and includes: • Arms A & B: o mBPI-SF assessments: includes the worst pain severity (item 3) and pain interference (item 9a) assessments.

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
• injection site pain								○ Pain medication usage. • Arm B only: ○ Injection site pain. • Evening daily diary by paper or electronic handheld device. If both versions are available, electronic version must be completed. • PROs mandatory unless the electronic devices are not available due to local restrictions. In this case completion of any PRO version including the paper version is not required. • See Section 8.9, Appendix 14

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
PRO Assessment*: • Patient preference questionnaire			X	X (only at Cycle 4)				• The patient preference questionnaire will be completed by the participants prior to any Day 1 procedure at Cycle 2 and Cycle 4. • Questionnaire by paper or electronic. If both versions are available, electronic version must be completed • PROs mandatory unless the electronic devices are not available due to local restrictions. In this case completion of any PRO version including the paper version is not required. • See Section 8.9, Appendix 14
Survival Follow-up							X	• Survival status will also include all FU anticancer therapies. • Survival may be collected also by telephone contact, email, etc. • See Section 7.1.1.2
Pharmacokinetic assessments to be shipped to the central laboratories								
Blood sample for PK (Arm A)*	See Table 3							

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Special Laboratory Studies to be shipped to the central laboratories								
ctDNA Blood Sample*		X	X	X (Cycle 6 only)	X			• Two samples of 10 mL of whole blood (one 10 mL whole blood sample for China) at each timepoint will be collected. C1D1 samples may also be used for the development of companion diagnostics, if needed. • Refer to Section 8.7.2 and Laboratory Manual.
Retained Research Blood Sample for genetics		X						• A single 4 mL whole blood sample for DNA extraction (Prep D1) will be collected, unless prohibited by local regulations, IRBs/ECs. • If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.6.2

Table 2. Study SoA

Protocol Activity	Screening[a]	Active Treatment Phase[b] (1 Cycle = 28 days)			EOT / Withdrawal[c]	Post-Treatment FU		Notes
		Cycle 1	Cycle 2	Cycles ≥3		Safety FU[d]	Survival FU[e]	a. **Screening**: screening procedures should be completed within 28 days from consent to randomization unless otherwise specified.
Study Day	**≤ 28 days**	**Day 1**	**Day 1**	**Day 1**		**28 days from last dose**	**Every 3 mos from the EOT**	b. **Active Treatment Phase** assessments should be performed, and safety assessments reviewed prior to dosing on the visit days, unless otherwise specified, using the following sequence (if performed on the same day): 1) PROs (with the exception of the evening daily diary); 2) ECGs; 3) blood drawn for PK; 4) blood drawn for lab tests/ctDNA/Retained Research Sample; 5) PE/Vital signs.
Visit Window (days)		**-2**	**±2**	**±2**		**+7**	**±14**	c. **EOT** assessments should be performed only if they have NOT been completed: 1) within the previous 4 weeks for safety assessments, unless needed for monitoring of safety findings; 2) within the previous timepoint for tumor assessments (8 or 12 weeks as per frequency of tumor assessments) or 24 weeks for bone scan if bone scan is the preferred technique to follow bone lesion/s on treatment and unless PD has been confirmed elsewhere.
								d. **Safety FU** is a minimum of 28 days from last dose OR prior to initiation of a new anticancer therapy, whichever comes first (Section 7.1.1.1).
								e. **Survival FU** is every 3 months from EOT (Section 7.1.1.2).
Tumor Tissue for Biomarkers	X (Mandatory)				X (optional)			• See Section 8.7.1

* Assessments may be performed during home health visits that will be allowed on a case-by-case basis. Confirmation from the sponsor will include which visits can be performed at home.

Table 3. Pharmacokinetic and ECGs, Schedule of Activities

Protocol Activity	**Active Treatment Phase (1 Cycle = 28 days)**							**Notes**
Study Day	**Screening**	**Cycle 1 Day 1**	**Cycle 2 Day 1**		**Cycle 3, 5 & 7 Day 1**		**EoT/Withdrawal**	On the visit days, participant should be instructed not to take ARV-471 dosing and to withhold their daily dose of ARV-471 until the pre-dose assessments have been completed. On the visit days assessments should be performed, unless otherwise specified, using **the following** sequence: ECGs, blood drawn for PK and blood drawn for lab tests.
Visit Window (days)			**±2**		**±2**			
Hours post dosing	**≤ 28 days**	**0 h (within 2.5 h prior to dose**)**	**0 h (within 2.5 h prior to dose**)**	**5-7 h**	**0 h (within 2.5 h prior to dose**)**	**5 -7 h**		
• ***Arm A: Participants in the QTc-Substudy and all the remaining participants in Arm A***								
12 Lead ECG (triplicate)*	X	X	X	X	X (Cycle 3 only)	X (Cycle 3 only)	X	• **For the participants in the QTc sub-study (approximately 80 participants enrolled at selected sites): at least 1-hour** fasting needed at all timepoints with the exception of screening. Central reading is required for all ECG timepoints apart from screening. • Triplicate ECG should be performed immediately before PK blood draws at respective time points. • ECG measurement required at any time between 5-7 hours after drug intake. • Blood sample for electrolytes (sodium, potassium, magnesium, total calcium) must be collected at Day 1 pre-dose (with a time window of -2 days) (see the note for sequence above if performed on the same day of ECG and PK). If not performed on Day 1, electrolytes must be repeated on Day 1 if ECG abnormalities are observed. • Refer to Section 8.3.3

Table 3. Pharmacokinetic and ECGs, Schedule of Activities

Protocol Activity	Active Treatment Phase (1 Cycle = 28 days)							Notes
Study Day	**Screening**	**Cycle 1 Day 1**	**Cycle 2 Day 1**		**Cycle 3, 5 & 7 Day 1**		**EoT/Withdrawal**	On the visit days, participant should be instructed not to take ARV-471 dosing and to withhold their daily dose of ARV-471 until the pre-dose assessments have been completed. On the visit days assessments should be performed, unless otherwise specified, using **the following** sequence: ECGs, blood drawn for PK and blood drawn for lab tests.
Visit Window (days)			**±2**		**±2**			
Hours post dosing	**≤ 28 days**	**0 h (within 2.5 h prior to dose**)**	**0 h (within 2.5 h prior to dose**)**	**5-7 h**	**0 h (within 2.5 h prior to dose**)**	**5 -7 h**		
Blood sample for PK*			X	X	X	X (Cycle 3 only)		• A single 3 mL whole blood sample will be collected at each time point. • Pre-dose PK samples should be collected within 2.5 hours prior to dosing. • PK samples will be shipped to the central laboratory. • Refer to Section 8.5
• ***Arm B***								
12 Lead ECG (triplicate)*	X	X	X		X (Cycle 3 only)		X	• Triplicate ECG is required at all time points. • Blood sample for electrolytes (sodium, potassium, magnesium, total calcium) must be collected at Day 1 pre-dose (with a time window of -2 days) (see the note for sequence above if performed on the same day of ECG and PK). If not performed on Day 1, electrolytes must be repeated on Day 1 if ECG abnormalities are observed). • Refer to Section 8.3.3

* Assessments may be performed during home health visits that will be allowed on a case-by-case basis. Confirmation from the sponsor will include which visits can be performed at home.

Table 3. Pharmacokinetic and ECGs, Schedule of Activities

Protocol Activity	Active Treatment Phase (1 Cycle = 28 days)							Notes
Study Day	**Screening**	**Cycle 1 Day 1**	**Cycle 2 Day 1**		**Cycle 3, 5 & 7 Day 1**		**EoT/Withdrawal**	On the visit days, participant should be instructed not to take ARV-471 dosing and to withhold their daily dose of ARV-471 until the pre-dose assessments have been completed. On the visit days assessments should be performed, unless otherwise specified, using **the following** sequence: ECGs, blood drawn for PK and blood drawn for lab tests.
Visit Window (days)			**±2**		**±2**			
Hours post dosing	**≤ 28 days**	**0 h (within 2.5 h prior to dose**)**	**0 h (within 2.5 h prior to dose**)**	**5-7 h**	**0 h (within 2.5 h prior to dose**)**	**5 -7 h**		

** The time window of 2.5 hours is strongly recommended; however, it may be extended up to 4 hours to accommodate site needs as long as all samples are collected on each evaluation day as per Table 3.

2. INTRODUCTION

ARV-471 (also known as PF-07850327 or vepdegestrant) is a potent, selective, orally bioavailable PROTAC, which is a small molecule that induces degradation of the ER. In this study (V**ER**ITAC-2) ARV-471 is being investigated in participants with ER(+), human epidermal growth factor receptor negative (HER2[-]) unresectable locoregional recurrent or mBC who have progressed after prior endocrine based treatment(s) for advanced disease.

The investigational drugs ARV-471 (PF-07850327) and fulvestrant will be identified throughout the protocol as ARV-471 and fulvestrant.

The study population, participants with unresectable locoregional recurrent or mBC, will be reported as participants with aBC throughout the protocol.

2.1. Study Rationale

The purpose of this study is to demonstrate the superiority of ARV-471 in terms of progression free survival compared to fulvestrant in participants with ER(+)/HER2(-) aBC who have progressed after prior endocrine based treatment(s) for their advanced disease.

The past decade has seen significant improvements in the treatment options for patients with advanced ER(+)/HER2(-) breast cancer. However, there is still an unmet need to improve clinical outcomes after progression with existing ET, particularly for the second- and third-line patients where the desire is to delay treatment with chemotherapy. ARV-471 may represent a potential alternative due to its unique mechanism of action that may have the advantage of achieving complete inhibition of the ER by essentially eliminating the entire protein. This may be particularly advantageous in the setting of constitutively active ESR1 mutations.

2.2. Background

2.2.1. Breast Cancer

Female breast cancer has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. BC is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths (Sung et al, 2021) and the second leading cause of cancer death in women, with over 43,250 women expected to die from the disease in 2022 in the US (Siegel et al, 2022). While BC is less common in men, men account for approximately 1% of all newly diagnosed cases, and almost 530 men are projected to die from their disease in 2022 (Siegel et al, 2022).

Globally, the number of people living with mBC is increasing, primarily because of improvements in available treatment options. In the US the estimated number of women living with mBC increased by 17% from 2000 to 2010 and was projected to increase by 31% from 2010 to 2020 (Mariotto et al, 2017). In this country the vast majority (approximately 73%) have HR+ and HER2(-) disease (Howlader et al, 2014).

Although age adjusted mortality from BC has been decreasing during the last decades, the median survival time for patients with metastatic disease is still approximately 18-24 months

and there remains urgent medical need for more active agents in this metastatic setting (Zheng et al, 2020).

2.2.2. Treatment Options for ER-positive Breast Cancer

Treatment options for patients with aBC depend on many different factors, including whether the tumors express hormone receptors (ER and/or progesterone receptor [PR]) or HER2. The standards of care for people with ER(+) aBC are ETs (ie, letrozole, anastrozole, exemestane, fulvestrant, tamoxifen), as a single agent or co-administered with targeted therapy (CDK4/6 inhibitors, PI3K inhibitors, mTOR inhibitors, and PARP inhibitors), and/or chemotherapy.

Targeting estrogen receptor signaling is a cornerstone of treatment for ER(+) breast cancer and has evolved over time from the use of selective ER modulators (tamoxifen) to aromatase inhibitors (letrozole, anastrozole, exemestane), and selective estrogen receptor degraders (SERDs, fulvestrant). More recently, combinations of endocrine therapy with molecularly targeted agents have further improved outcome of patients (McAndrew & Finn, 2021).

Despite the significant clinical benefit, patients still develop endocrine resistance after or during endocrine treatment. Endocrine resistance is a clinical challenge and can present at diagnosis (de novo/intrinsic resistance) or after treatment with endocrine therapy (acquired resistance). Intrinsic resistance is thought to be present in up to 30% of patients and due to lack of expression of ER (Belachew & Sewasew, 2021). 30-50% of patients will develop SERD/SERM/AI-resistant ER-positive metastatic lesions after an average of 5 years (Fanning & Greene, 2019; Rozeboom et al, 2019).

2.2.3. ARV-471

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

In non-clinical studies, ARV-471 demonstrated in vitro potent (< 1 nM) and robust (> 90%) ER degradation even in the presence of clinically relevant, mutated (Y537S and D538G) forms of ER. Based on non-clinical studies, ARV-471 may have advantages over fulvestrant and other oral SERDs in clinical development such as RAD1901/elacestrant (Flanagan et al, 2018). While SERDs destabilize ER and indirectly lead to ER degradation, ARV-471 actively degrades ER, which may lead to less drug resistance. In vivo, ARV-471 inhibits tumor growth in multiple mouse xenograft models. Notably, ARV-471 demonstrates superior TGI compared to fulvestrant in a Y537S ESR1 *mutant* patient-derived xenograft model (ARV-471 IB). In the MCF7-xenograft mouse model, 3 to 30 mg/kg ARV-471, orally administered to mice once daily for 28 days, displayed dose-dependent efficacy with doses of 3 and 10 mg/kg/day inhibiting tumor growth by 85% and 98%, respectively, and 30 mg/kg/day leading to tumor shrinkage (124% TGI). At study termination, the tumor ER levels were reduced by ≥ 94% suggesting that higher doses are required for maximal efficacy than for maximal ER degradation.

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

2.2.3.1. Non-clinical Pharmacokinetics and Metabolism

ARV-471 is a BCS Class IV compound (low solubility/low permeability). The PK profile of ARV-471 in the nonclinical species (mouse, rat, dog, and monkey) was characterized by a low to moderate clearance (13.8% to 33.8% of hepatic blood flow), extensive tissue distribution (2.1 to 6.0 L/kg), short to moderate half-life of elimination ($T_{1/2}$) (2.1 to 8.2 hours), and moderate to good oral bioavailability (27% to 65%). ARV-471 can interconvert to its epimer, ARV-473 (ARV-471 IB).

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

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

CYP3A4 is the main isoform contributing to ARV-471 CYP metabolism (accounting for 85% of CYP metabolism).

2.2.3.2. Potential Drug-Drug Interactions

Drugs that are inhibitors of CYP3A4 may increase the exposure of ARV-471, whereas drugs that are inducers of CYP3A4 may reduce the exposure of ARV-471.

In vitro, ARV-471 is an inhibitor of CYP2B6 with an IC_{50} of 16.0 μM. However, subsequent mechanistic static modeling, using bupropion as the probe CYP2B6 substrate drug, indicated a low potential for DDI due to ARV-471-mediated reversible inhibition of CYP2B6 at human exposures associated with the 500 mg QD dose. Since bupropion is the only known sensitive CYP2B6 substrate, participants enrolled in clinical trials are allowed to receive CYP2B6 substrates or CYP2B6 substrates with narrow therapeutic indices.

ARV-471 showed weak inhibition of human BCRP and is considered an in vitro inhibitor of P-gp. Based on the lack of significant safety issues when a sensitive BCRP substrate, rosuvastatin, was administered together with ARV-471 in study ARV-471-mBC-101, participants enrolled in clinical trials will be allowed to receive sensitive BCRP substrates or BCRP substrates with narrow therapeutic indices. Clinical DDI studies with P-gp substrates have not yet been conducted (ARV-471 IB).

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. Effect of PPI on ARV-471 in healthy participants was evaluated in Study ARV-471-CPhm-103. Preliminary results demonstrated that ARV-471 AUC values were similar when administered with PPI or without PPI, although PPI decreased median ARV-471 C_{max} about 18% which is not considered clinically meaningful. This indicates that

there are no effects of PPI on exposure of ARV-471 when administered with a moderate fat meal. 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. Administer ARV-471 ≥2 hours before or after antacids. Administer ARV 471 ≥2 hours before or 10-12 hours after H_2 receptor antagonists (ARV-471 IB).

2.2.3.3. ARV-471 Preliminary Safety, Efficacy and PK in Humans

In the ongoing FIH Study [ARV-471-mBC-101], ARV-471 is being assessed as a monotherapy and in combination with palbociclib in participants with ER(+)/HER2(-) aBC who had previously received CDK4/6 inhibitors and/or endocrine therapy and/or chemotherapy in the locally advanced/metastatic setting. The FIH study has 3 parts: Part A is a monotherapy dose escalation, Part B is a monotherapy dose expansion (200 mg or 500 mg, oral daily dosing), and Part C is evaluating the combination of ARV-471 and palbociclib (ARV-471 at 180, 200, 400 and 500 mg oral daily dosing plus palbociclib at 125 mg oral daily for 3 consecutive weeks followed by 1 week off treatment). As of 06 June 2022, 176 participants have been treated in the FIH study (Part A n=78; Part B n=71, Part C n=27) (ARV-471 IB).

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

In **Part A** (monotherapy dose escalation), a total of 71 out of the 78 participants (91.0%) reported at least 1 TEAE. The most common TEAEs (regardless of attribution to study drug) observed in ≥10% of participants were: fatigue (33%), nausea (33%), constipation (31%), arthralgia (18%), vomiting (18%), back pain (17%), diarrhea (17%), headache (17%), decreased appetite (15%), AST increase (14%), hot flush (14%), hyperglycemia (13%), pain in extremity (13%), insomnia (11%), ALT increased (10%), and dizziness (10%).
Most of the patients experienced Grade 1 or 2 TEAEs (74.3%), with Grade ≥3 occurred in 16.6% of patients.

The Grade 3 TEAEs were hypertension (2 patients) and nausea, stomatitis, arthralgia, fatigue, aspartate aminotransferase increased, electrocardiogram QT prolonged, amylase increased, blood alkaline phosphatase increased, lipase increased, headache, presyncope, embolism, embolism venous, procedural pain, humerus fracture, acute kidney injury, and malignant pleural effusion (1 patient each). The Grade 4 TEAEs of hypoglycemia, neutrophil count decreased, and neutropenia occurred in 1 patient each. The Grade 5 TEAE of cardiac arrest occurred in 1 patient and was unrelated to ARV-471.

A total of 54 participants (69%) had at least 1 TEAE considered potentially related to ARV-471. The most frequently (≥10% participants) reported treatment-related AEs (all grades) were nausea (26%), fatigue (22%), constipation (13%), arthralgia (10%), decreased appetite (10%), hot flush (10%), and vomiting (10%). Most participants experienced Grade 1 or 2

TRAEs (64.1%). Grade 3 TRAEs (5.1%) were headache, asymptomatic amylase and lipase increased, nausea and asymptomatic electrocardiogram QT prolonged, and venous embolism. There were no Grade 4 or Grade 5 TRAEs.

Safety profile from Part B (monotherapy dose expansion) is consistent with what has been observed in Part A (monotherapy dose escalation).

In **Part B**, a total of 62 of the 71 participants (87.3%) reported at least 1 TEAE. The most commonly reported TEAEs observed in ≥10% of participants include fatigue (39%), nausea (21%), constipation (17%), arthralgia (17%), AST increased (13%), back pain (11%), decreased appetite (11%), and headache (11%).

Most participants experienced Grade 1 or 2 TEAEs (64.8%) with Grade ≥3 occurred in 22.5% of patients. The Grade 3 TEAEs were anemia (2 patients) and intestinal obstruction, muscular weakness, aspartate aminotransferase increased, alanine aminotransferase 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 (1 patient each). The Grade 4 TEAEs of hyperbilirubinaemia, hypercalcaemia and hepatic haemorrhage were reported in 1 patient each. A Grade 5 TEAE of acute respiratory failure was reported in 1 patient, after that patient presented with progressive malignant pleural effusion.

A total of 51 participants (71.8%) experienced at least 1 TRAE. The most common TRAEs, observed in ≥10% of participants include fatigue (34%), nausea (17%), and arthralgia (13%). Most participants experienced Grade 1 or 2 TRAEs (64.8%). Grade 3 events (7.0%) of electrocardiogram QT prolonged, thrombocytopenia, neutropenia, decreased appetite, and fatigue were experienced by 1 patient each. There was one Grade 4 TRAE of hyperbilirubinaemia. There were no Grade 5 TRAEs reported.

Based on preliminary safety data from patients treated with ARV-471 in combination with palbociclib **(Part C)**, the combination appears tolerable. Part C is ongoing and as of 06 June 2022 a total of 24 of 27 participants (88.9%) reported at least 1 TEAE. The most common TEAEs observed in ≥20% of participants included neutrophil count decreased (51.9%), fatigue (44.4%), neutropenia (37.0%), platelet count decreased (33.3%), anemia (29.6%), nausea (25.9%), cough (22.2%), diarrhea (22.2%), and WBC decreased (22.2%).

There have been 17 deaths reported in the ARV-471-mBC-101 study: 11 in Part A and 6 in Part B. None of these deaths were attributable to ARV-471. No deaths have been reported in Part C.

There was evidence of preliminary clinical activity in the Part A monotherapy dose escalation of Study ARV-471 mBC-101, with several patients achieving clinical benefit as defined by CBR and ORR as of 06 June 2022. CBR (rate of confirmed CR, PR, orSD ≥24 weeks) was 36.2% (95% CI: 25.0 - 48.7) in 25 of 69 evaluable participants; the ORR was 8.6% (95% CI: 2.9 -19.0), with 5 of 58 response-evaluable participants having confirmed PR (ARV-471 IB). No clear dose-dependent or exposure-response relationship for CBR was

observed, with exception of patients with ESR1 mutations showing a trend (not statistically significant) toward higher CBR with higher ARV-471 exposure (Arvinas, 2022).

In Part B dose expansion the CBR in the overall population was 37.1% (95% CI: 21.5%, 55.1%) and 38.9% (95% CI: 23.1%, 56.5%) at 200 mg and at 500 mg respectively. The CBR in evaluable patients with estrogen receptor 1 gene (ESR1) mutations, was similar between the doses: CBR was 47.4% in patients at 200 mg QD (95% CI: 24.4%, 71.1%) and 54.5% at 500 mg QD (95% CI: 32.2%, 75.6%). No exposure-response relationship for CBR was seen in the overall patient population or the ESR1 mutant patient population (Arvinas, 2022).
Clinical benefit (by CBR) was observed in CDK4/6 inhibitor-pretreated patients with ER(+)/HER2(-) BC in all Part A and B dose cohorts.
Efficacy data collection is ongoing Part C.

Preliminary PK data following single and multiple dosing from Part A monotherapy dose escalation of Study ARV-471-mBC-101 are available in mBC participants receiving ARV-471 at total daily dose levels ranging from 30 mg to 700 mg (administered either as QD or BID) under fed conditions. The median T_{max} ranged from 4 to 7 hours across the dose levels. The mean effective $t_{1/2}$ at steady state ranged from 23 to 33 hours. Clinical exposure of ARV-471 on Day 15 at 60 mg QD (geometric mean AUC_{tau} 7324 ng.h/mL) has exceeded the nonclinical efficacious exposure associated with TGI (AUC_{inf}=5,717 ng•h/mL) at 30 mg/kg single dose in mice. Following 200 mg QD dosing (N=8), a geometric mean accumulation ratio for AUC_{tau} of 1.7 was observed between Day 1 and Day 15. ARV-471 can interconvert to its epimer, ARV-473. The ratio of ARV-473 / ARV-471, based on AUC_{tau}, on Cycle 1 Day 15 is 32%.
Preclinical data showed ARV-471 has both antagonist and degradation activities against ER, whereas ARV-473 displays only antagonist activity (ARV-471 IB).

Safety and PK data in healthy volunteers is based on the Phase 1 clinical pharmacology study, Study ARV-471-CPhm-103, which is evaluating the effect of food or a PPI (esomeprazole) and the relative bioavailability of different tablet formulations on the single-dose PK and safety of ARV-471 in healthy postmenopausal female volunteers. As of data cut-off date of 16 June 2022, a total of 47 healthy participants have been treated in Study ARV-471-CPhm-103 (14 participants in fed/fasted, 17 participants in PPI, and 16 participants in rBA portions). Each participant received 2 doses of 200 mg ARV-471, 1 in each of the 2 periods, and the ARV-471 treatments were separated by a washout period of at least 14 days. Preliminary analysis results showed the median T_{max} ranged from 6.0 to 8.0 hours across the cohorts. The geometric mean $t_{1/2}$ following a single 200 mg dose was about 40 hours under fed condition. Food intake significantly increased ARV 471 C_{max} and AUC_{inf} 3- to 2- fold, respectively, as compared with fasted conditions. Thus, patients should be instructed to take ARV-471 with food. ARV-471 AUC values were similar when administered with PPI or without PPI when given with a moderate-fat meal, although PPI decreased ARV-471 C_{max} about 18% which is not considered clinically meaningful.

Analysis of 14 paired biopsies from patients treated in Part A (monotherapy dose escalation) at various doses of ARV-471 suggest robust ER degradation (up to 89% decrease, with a median ER decrease of 67%, [range: 21%, 89%])) across all doses up to 500 mg QD,

regardless of ESR1 mutation status with no apparent relationship between dose or exposure and ER degradation in patients with wild-type or mutant ER (Hamilton et al, 2022).

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

2.2.3.4. QTc Evaluation Data

Nonclinical data in dogs identified an approximate 13 msec prolongation of QT/QTc intervals at 90 mg/kg/day on Day 85 (nonadverse) of a 3-month dog toxicology study associated with comparative exposure margins to the 200 mg clinical dose of approximately 5.8x and 5.9x for AUC and C_{max}, respectively. Both single- and repeat-dose studies up to Day 28 were negative for this effect at higher or equivalent dose/exposures. 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.

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). From the ongoing ARV-471-mBC-101 study, as of 06 Jun 2022, 13 participants reported TEAEs of electrocardiogram QT prolonged (12 participants had TRAEs and in 1 participant the AE was considered as not related to ARV-471 per investigator). Most participants experienced grade 1 or 2 QT prolonged events (11 out of 13), two patients reported Grade 3 events and no Grade 4/5 have been reported. No QT prolonged events were reported as serious.

An external cardiology consultant review, including evaluation of the patient study treatment, laboratory and medical history as well as study ECGs, concluded that of the 13 participants who were reported to have experienced QTc prolonged events, only 2 participants had a true diagnosis of QTc prolongation, of which low potassium and concomitant medications were confounding factors.

Concentration-QTc modeling analysis of data from the ongoing ARV-471-mBC-101 study revealed a concentration-dependent increase in QTcF. Based on the model, a QTcF change from baseline is predicted to be 6.8 msec (90% CI: 5.7, 7.9) at the geometric mean C_{max} for the sum of ARV-471 and ARV-473 (1,091 ng/mL) at steady-state after 200 mg QD dosing. (ARV-471 IB)

2.2.3.4.1. QTc Sub-study

In order to characterize the effect of ARV-471, a QTc sub-study will be conducted in a sub-set of participants in Arm A in this study at selected sites. To control potential significant confounding factors, concomitant use of ARV-471 with drugs of known risk of causing QT interval prolongation or Torsade de Pointes are prohibited or should be used with caution

(Section 6.9.3 and Appendix 10). The QTc interval via triplicate ECGs with time-matched PK draws (See Table 3 and Section 8.3.3) will be evaluated.

2.2.4. SERD

Fulvestrant is given as an intramuscular injection in a clinical setting and inhibits estrogen signaling through the ER primarily in 2 ways: 1) competitive inhibition of estradiol binding to the ER, blocking nuclear localization, and 2) accelerated degradation of the ER protein due to the instability of the fulvestrant-ER complex. After fulvestrant treatment, ER declined significantly compared to pre-treatment reaching its lowest levels at 6 months (6-mos median ER Hscore of 48 [2-135] versus pretreatment median ER Hscore of 130 [60-190]). This ER level was generally maintained at time of fulvestrant progression (median ER Hscore of 50 [8-130]) showing that no patient had lost all ER at relapse even in the longest interval between treatment and progression of 60.7 months, indicating a need for more effective ER-degrading molecules (Agrawal et al, 2016).

In this study, PFS improvement with ARV-471 over fulvestrant is expected in participants pretreated with endocrine-based treatment in view of the clinical data currently available for monotherapy fulvestrant. Fulvestrant has demonstrated activity in patients with both wild-type and ESR1 mutant tumors in the second line treatment setting with 4.1 months (95% CI, 3.6-5.5) mPFS in patients with ESR1 wild type tumors and 3.9 months (95% CI, 3.0-6.0) mPFS in patients with ESR1 mutant tumors (Turner et al, 2020). However, the clinical benefit reported in participants whose disease progressed after CDK4/6 inhibitor + ET therapy treated with fulvestrant (1.94 months mPFS [95% CI, 1.84–3.55] in the VERONICA study) (Lindeman et al, 2021) or with standard treatments (3.5 months mPFS [95% CI, 3.0–5.4] in the ByLieve study) (Rugo et al, 2021) did not show robust enhancement and needs to be further improved. In this setting, SERDs are one of the treatments currently under investigation against aromatase inhibitor- or tamoxifen-resistance.

Recent investigational advances have allowed the development of new orally bioavailable SERDs, with elacestrant being approved by FDA and EMA in 2023. In a Phase 3 study, elacestrant, , has demonstrated a statistically significant improvement in PFS over SOC (ie AIs or fulvestrant) in participants with ER(+)/HER2(-) aBC in the second- and third-line settings. Approximately half of the participants enrolled had BC that harboured ESR1 mutations. The study results showed a statistically significant improvement of mPFS in the elacestrant arm compared to SOC in all participants with a median PFS of 2.79 vs 1.91 months (HR=0.697 [95% CI: 0.552, 0.880]; P=0.0018) and in participants with ESR1 mutant BC with 3.78 vs 1.87 months mPFS (HR=0.546 [95% CI: 0.387, 0.768]; P=0.0005). Preliminary OS data, although not yet mature, demonstrated a trend in favor of elacestrant in all participants (HR=0.751 [95% CI: 0.542, 1.038]; P=0.0821) and in participants with ESR1 mutant BC (HR=0.592 [95% CI: 0.361, 0.958]; P=0.0325) (Bardia et al, 2022). These data support the rationale for assessing ARV-471 in this patient population.

Currently, there is a gap in high-level evidence on the optimal sequencing of agents after progression on CDK4/6 inhibitors in the frontline setting. Unanswered questions include what is the efficacy of using CDK4/6 inhibitors beyond progression and what is the efficacy

of other therapies after progression, given the fact that most of the data generated with older regimens occurred in the era before CDK4/6 inhibitors were broadly used (McAndrew & Finn, 2021).

The development of ET-resistant phenotypes involves multiple mechanisms. These include (a) ERα mutations (where ESR1 gene mutations are one of the most studied) that lead to ligand-independent constitutive activation of ER, (b) in the absence of estradiol, the activation of ERα because of signaling pathway activation and (c) variation in the expression of ERα cofactors responsible for the ERα modulator activity. Investigation of potential mutations is highly recommended after progression, especially for PIK3CA and ESR1 mutations, the most common mechanisms of acquired resistance to ET. ESR1 mutation may occur with an approximate 20-40% prevalence after progression on an AI (Brett et al, 2021).

2.3. Benefit/Risk Assessment

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

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

Potential risks of clinical significance and procedures are listed in the table below.
These may include known or potential adverse events of study interventions based on:

- Observations in ARV-471 nonclinical studies, early clinical studies, or non-toxicological studies
- ARV-471's mechanistic similarity to endocrine therapy, including SERDs

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. Thirteen participants were reported with non-serious AE of QT interval prolongation in the ongoing FIH study (ARV-471-mBC-101; Parts A, B and C) snapshot date of 06 June 2022, n=176); 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 intervention period (Table 2). Participants at high risk of QT prolongation as per EC #5 are excluded from participation in the study (see Section 5.2). Concomitant drugs predisposing to Torsade de Pointes or QT prolongation are excluded or used with caution as per Section 6.9.3 and Appendix 10. Study intervention will be temporarily interrupted, reduced, or permanently discontinued based on severity of the events occurred (see Section 6.6.2).
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	Participants with a history of clinically significant thromboembolic or cerebrovascular events are excluded from participation in the study as per EC #5 (see Section 5.2). Coagulation tests will be performed at screening and will be repeated on treatment as needed. Suspicious of VE should be investigated, per local standard practice (eg, D-Dimer, fibrinogen, imaging).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	investigator, were reported in the FIH Study ARV-471-mBC-101.	Study intervention will be temporarily interrupted, reduced, or permanently discontinued based on severity of the events occurred (see Section 6.6.2).
Developmental and reproductive toxicities	Based on mechanism of action. The loss of estrogen signaling leads to alterations estrogen signaling leads to alterations in the hormonal input and feedback loops that are necessary for the menstrual cycle (humans or estrus in animals) and for the maintenance of pregnancy. The summary of the non-clinical animal findings included: Developmental (Embryo-Fetal) Toxicities. In 1-month rat study: loss of ability to maintain pregnancy, fetal death observed. Reproductive Toxicities in animal studies: Adverse microscopic changes in female tissues that impact organ function; Leydig cell hyperplasia and prostate changes in males; Clear impact on female fertility, potential risk for male fertility ARV-471 may cause fetal loss or reproductive abnormalities when administered to the pregnant woman or WOCBP.	Protocol inclusion criteria specify allowable menopausal status and mitigations. . Pregnant participants or participants <18 years are excluded in the clinical study protocols. Risk minimization measures have been implemented, including 1) the requirement for LHRH agonist use for pre-/peri-menopausal women prior to and during treatment and 2) the requirement for ensuring highly effective contraceptive measures for WOCBP and for male participants with WOCBP partners.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical finding showed that no developmental or reproductive toxicities have been reported to date.	
Study Intervention(s) Fulvestrant		
• thromboembolic events • injection site AEs (eg, sciatica, neuralgia, neuropathic pain, and peripheral neuropathy, risk of bleeding). • Osteoporosis • Increased exposure in patients with hepatic impairment	The potential risks are based on the Faslodex EU SmPC for fulvestrant.	Participants with a history of clinically significant thromboembolic events are excluded from participation in the study as per EC #5 (see Section 5.2). Coagulation tests will be performed at screening and will be repeated on treatment as needed. Injection will be completed by qualified and trained medical personnel and appropriate medication will be administered based on the severity of the AE. Calcium level will be assessed at screening and during the study and supportive care (eg, Bisphosphonate or RANKL inhibitors) will be administered as needed. Hepatic parameters will be collected at screening and during the study intervention.
Study Procedures		
Tumor biopsy requested for inclusion and end of treatment	Risks associated with any tumor biopsy include the following: • Pain from local anesthetic. • Pain/discomfort from biopsy procedure. • Bleeding, swelling, scarring, pain or bruising at the biopsy site. • Infection of wound. • Biopsies of certain sites may increase chances of life-threatening complications, eg pneumothorax during biopsy of lung.	All procedures will be completed by qualified and trained medical practitioners. Local anesthetic will be administered. Sterile technique will be used. Participants should not be subjected to a significant risk procedure to obtain biopsies. EOT biopsy (optional) will be collected only in participants who progressed, if clinically feasible.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Blood sample collections for safety assessment, pharmacokinetics and biomarkers	A blood draw may cause inflammation of the vein, pain, bruising, discomfort, redness, burning, or bleeding at the site where the needle is placed to draw the blood. May cause participant to feel dizzy or faint. There is a slight chance of infection.	All blood draws will be completed by qualified and trained medical personnel. Sterile technique will be used. Blood sample collections will be conducted at facilities prepared for adverse reactions related to the collection.
Participants will have CT/MRI scans and bone scans during study participation	CT scans expose participants to small doses of radiation Contrast dye used for CT scans may cause pain or burning upon injection, may worsen kidney function in participants with kidney disease and may cause allergic reactions that could be severe and life-threatening. Radioactive material for bone Scan may cause pain or burning upon injection.	Radiation exposure during the study will slightly exceed what a participant would receive under SOC and should not create a significant risk to health. Participants with renal function impairment are excluded (EC#13) (see Section 5.2). CT scans will be conducted at facilities prepared for adverse reactions to the contrast dye. Hydration and/or premedication prior to contrast media administration or steroids administration in case of allergic reactions may to be instituted as per local standard practice. A bone scan exposes participants to a small dose of radiation that should not create a significant risk to health.
Medical Device		
Fulvestrant administration using prefilled-syringe	Medical devices non-conformities Malfunction	Sponsor will provide high quality medical Prefilled Filled Syringe devices Study staff will be instructed to report any medical device deficiencies to the sponsor as reported in the Section 8.4.9 and Appendix 9.
Decentralized/telehealth interactions study assessments may impact outcome assessments.	Decentralized study/telehealth study assessments may increase the chance of missing data. Vital signs and a physical examination will not be performed for telehealth interactions, which may increase the	Training will be provided to all parties involved in study conduct on data acquisition tools, including those used in home health visits, and their role/responsibilities to ensure complete and correct data flow. Home heath visits will be performed by a registered nurse/other qualified health care provider and the investigator or designee must be available for consultation. If required by local regulations home heath visits will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	chance of not capturing clinically relevant information.	performed by the investigator or by a physician designee for specific assessments (eg, fulvestrant intramuscular administration, physical examinations and collection of adverse events).

2.3.2. Benefit Assessment

In non-clinical studies ARV-471 demonstrated a potent (<1 nM) and robust (>90%) ER degradation, even in the presence of clinically relevant ER mutations (ARV-471 IB). ARV-471 has demonstrated greater ER degradation compared to other novel SERDs in clinical development such as elacestrant/RAD1901 (Flanagan et al, 2018). In vivo, ARV-471 inhibits tumor growth in multiple mouse xenograft models including ESR1 *mutant* patient-derived xenograft model as single agent or in combination with palbociclib (Flanagan et al, 2018).

Preliminary clinical data from the ongoing FIH ARV 471-mBC-101 study Part A demonstrated that ARV-471 has antitumor activity (CBR of 36.2% [95% CI: 25.0–48.7] and ORR 8.6% [95% CI:2.9 - 19.0]) (ARV-471 IB).

In Part B dose expansion the CBR in the overall population was 37.1% (95% CI: 21.5%, 55.1%) and 38.9% (95% CI: 23.1%, 56.5%) at 200 mg and 500 mg QD, respectively. Overall, no exposure-response relationship for CBR was seen in the overall patient population or the *ESR1* mutant patient population. Clinical benefit (by CBR) was observed in CDK4/6 inhibitor-pretreated patients with ER+/HER2- BC in all Part A and B dose cohorts (Arvinas, 2022). In this study ARV-471 has shown robust ER degradation (up to 89% decrease with a median decrease of 67%, [range: 21% - 89%]) observed across doses up to 500 mg daily, regardless of ESR1 mutation status (Hamilton et al, 2022). Safety data from the ongoing FIH ARV 471-mBC-101 study demonstrated that ARV-471 is safe and well tolerated all the tested doses (Hamilton et al, 2022).

2.3.3. Overall Benefit/Risk Conclusion

Preliminary data from the ongoing FIH Phase 1 ARV-471-mBC-101 study suggest that ARV-471 has the potential to provide clinical benefit to participants with ER(+)/HER2(-) aBC.

ARV-471 has been found to be safe and well-tolerated in the ongoing FIH study, up to a total daily dose of 700 mg. Coupled with the data from non-clinical studies, the risk of clinically significant toxicities in this study is assessed as low. In addition, ARV-471 was active in non-clinical models harboring clinically relevant ESR1 mutations associated with resistance to ET, including superior TGI compared to fulvestrant in a Y537S ESR1 *mutant* patient-derived xenograft model. Preliminary clinical data from the ongoing FIH ARV 471-mBC-101 study Part A demonstrated that ARV-471 has antitumor activity (CBR of 36.2% [95% CI: 25.0–48.7] and ORR 8.6% [95% CI:2.9-19.0]) (ARV-471 IB). In Part B dose expansion the CBR in the overall population was 37.1% (95% CI: 21.5%, 55.1%) and 38.9% (95% CI: 23.1%, 56.5%) at 200 mg and 500 mg QD, respectively. Overall, no exposure-response relationship for CBR was seen in the overall patient population or the *ESR1* mutant patient population (Arvinas, 2022).Clinical benefit (by CBR) was observed in CDK4/6 inhibitor-pretreated patients with ER+/HER2- BC in dose escalation and expansion cohorts (ARV-471 IB).

Taken together, these data show that ARV-471 may represent an important therapeutic option for participants with ER(+)/HER2(-) aBC who have progressed after prior endocrine-based treatment(s) for their advanced disease.

Given current data, the anticipated benefits that may be afforded to participants with ER(+)/HER2(-) advanced breast cancer outweigh the potential risks identified in association with ARV-471. The clinical program will continue to monitor the benefit/risk profile of ARV-471.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To demonstrate that ARV-471 is superior to fulvestrant in prolonging PFS by BICR assessment in participants with ER(+)/HER2(-) aBC (all participants and participants with ESR1 mutation-positive BC) who have received prior endocrine-based treatment for their advanced disease	• PFS, defined as the time from the date of randomization to the date of first documented disease progression, as determined by BICR assessment per RECIST v1.1, or death due to any cause, whichever occurs first	• The primary estimand is to compare the treatment effect (as measured by HR) of ARV-471 versus fulvestrant on PFS in participants with ER(+)/HER2(-) aBC (all participants and participants with ESR1 mutation-positive BC) who have received prior endocrine-based treatment for their advanced disease. PFS will be analyzed using the stratified log-rank test and Kaplan-Meier method. PFS data will be censored for those who did not have a PFS event, discontinued the study treatment due to withdrawal of consent prior to an event, started a new anti-cancer therapy prior to an event, had an event after an unacceptably long interval, or lost to follow-up.
Key Secondary:	**Key Secondary:**	**Key Secondary:**
• To demonstrate that ARV-471 is superior to fulvestrant in prolonging overall survival (all participants and participants with ESR1 mutation-positive BC)	• OS, defined as the time from the date of randomization to the date of death due to any cause	• The estimand for OS is to compare the treatment effect (as measured by HR) of ARV-471 versus fulvestrant in participants with ER(+)/HER2(-) aBC (all participants and participants with ESR1 mutation-positive BC) who have received prior endocrine-based treatment for their advanced disease. OS will be analyzed using the stratified log-rank test and Kaplan-Meier method. OS data will be censored for those who did not have an OS event.
Secondary:	**Secondary:**	**Secondary:**
• To compare measures of tumor control between treatment arms and to evaluate the DOR by BICR assessment within each treatment arm	• OR: confirmed CR or PR by BICR assessment • CBR defined as confirmed CR or PR at any time or SD or non-CR/non-PD ≥24 weeks by BICR assessment • DOR by BICR assessment	• Not applicable.

Objectives	Endpoints	Estimands
• To evaluate safety and tolerability between the treatment arms	• Type, incidence, severity (as graded by NCI CTCAE v5.0), seriousness and relationship to study medications of AEs and any laboratory and ECG abnormalities	• Not applicable.
• To characterize the effects of ARV-471 on QTc	• QTc	• Not applicable.
• To evaluate patient reported outcomes between two treatment arms	• EORTC QLQ-C30 • EORTC QLQ-BR23 • EuroQol; EQ-5D-5L • BPI-SF	• Not applicable.
• To determine plasma concentrations of ARV-471 and ARV-473 after repeated dosing of ARV-471	• Plasma concentrations of ARV-471 and its epimer ARV-473	• Not applicable.
• To assess changes from baseline levels in plasma ctDNA	• ctDNA plasma quantitative changes from baseline to evaluate their associations with clinical outcomes	• Not applicable.
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To evaluate correlations of biomarkers with ARV-471 exposure, efficacy and other clinical outcomes	• Tumor tissue and/or blood biomarkers, to determine gene mutations (eg, ESR1, PIK3CA), and cell proliferation and oncologic driven proteins (eg, Ki67) involved in the biology aBC, mechanisms of resistance of ARV-471	• Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This is an international Phase 3 multicenter, randomized, open-label, parallel-group study aimed to demonstrate that ARV-471 is superior to fulvestrant in prolonging the progression-free survival (PFS by BICR assessment) in participants with ER(+)/HER2(-) aBC who have progressed after prior endocrine treatment-based regimen(s) for advanced disease.

Approximately 560 participants (of which approximately 280 are participants with ESR1 mutation) will be randomly assigned to Arm A (ARV-471) or Arm B (fulvestrant). Enrolment will continue until approximately 280 participants with the ESR1 mutation have been enrolled.

Participants will be randomly assigned on a 1:1 basis to:

- Arm A: (Investigational Arm; n ≈ 280). Participants will receive ARV-471 200 mg orally, once daily on a 28-day continuous dosing schedule.

- Arm B: (Comparator Arm; n ≈ 280). Participants will receive fulvestrant 500 mg, intramuscularly on Days 1 and 15 of Cycle 1 and then on Day 1 of each cycle starting from C2D1 (28-day cycle).

Information on ARV-471 dose and administration is provided in Table 4 and Section 6.1.1.1. Details on dose modifications for toxicity for ARV-471 are provided in Section 6.6.2.

Information on fulvestrant dose and administration is provided in Table 4 and Section 6.1.1.2. Dose reduction of fulvestrant is not permitted (See Section 6.6.1).

Analysis of ctDNA samples for ESR1 status evaluation (wild-type versus ESR1 mutated) will be performed (refer to the Laboratory Manual for specific information) during the pre-screening period. Participants are required to give consent during the pre-screening period prior to collection of ctDNA samples sufficient for assessment or asking for approval to use an available ESR1 status result.

Screening activities may be performed while waiting for ESR1 test results/approval of prior ESR1 status, but ESR1 status must be available before randomization. The sponsor will monitor the frequency of the ESR1 status (wild-type or mutated) across the study population (see Section 9.5) to evaluate the proportion of wild-type or mutated ESR1 status (targeting approximately 280 participants with wild type ESR1/280 participants with mutated ESR1).

Sponsor approval for use of a previously performed test (with the exception of participants in China) may be obtained if all of the following criteria are met:

- The test result confirms ESR1 mutated status (will not be accepted for wild-type status results)
- Result is provided using an FDA approved test using ctDNA/tumor sample
- Participant's ctDNA sample/tumor sample was collected within 6 months from randomization in the current study.

The samples may be also used for development of companion diagnostics.

Participants will be stratified by:

- ESR1 mutational status (*Mutant*, Yes/No)
  In the event the ESR1 test is not informative (ie, test performed but the result is "unknown") the participant will be stratified as participant with *Mutant* "NO"

- Visceral disease: (Yes/No)
  Visceral refers to lung, liver, brain, pleural, and peritoneal involvement.

Pre- and peri-menopausal female and male participants must receive therapy with an LHRH agonist starting on Cycle 1 Day 1 (if not already on treatment) and continued during the study as per Table 2.

Participants will continue to receive assigned treatment until objective disease progression as per Section 7.1, unacceptable toxicity, death, participant refuses further treatment, or one of the other reasons for treatment discontinuation outlined in Section 7.1 is met. However, participants may continue treatment in the arm assigned at randomization beyond the time of RECIST-defined PD at the discretion of the investigator if that is considered to be in the best interest of the participant and as long as no new anticancer treatment is initiated (see Section 8.2.1.1). In this case, the participant should continue with routine safety and efficacy assessments as per the Table 2.

Crossover between treatment arms will NOT be allowed.

Participants will undergo efficacy assessments as outlined in Table 2. Efficacy analyses will be performed using the BICR tumor assessments as the primary data source. BICR will perform the review as per Section 8.2.1.2. All radiographic images as well as other information as per section 8.2.1.2 will be collected and objectively verified by BICR as described in the Study Imaging Manual.

Safety will be monitored at regular intervals through the study by laboratory tests and clinical visits as described in Table 2.

In Arm A, blood samples for pharmacokinetics analysis of ARV-471 and its epimer, ARV-473, will be collected. These samples will also be used for exposure/response analysis for safety and efficacy findings. For additional details on the PK sample collections, refer to Table 3 and Section 8.5.

The study includes a QTc sub-study in approximately 80 participants in Arm A enrolled at selected sites which will evaluate the effect of ARV-471 on QTc interval via triplicate ECGs (central reading) time-matched with PK draws (See Table 3 and Section 8.3.3).

PRO assessments will be administered to evaluate the impact on quality of life, functioning, symptoms, and general health status using the EQ-5D-5L, Quality of Life questionnaires, both general cancer and breast specific (EORTC QLQ-C30), EORTC QLQ-BR23 (female and male questionnaire versions), and the BPI-SF. The mBPI-SF (worst pain severity [item 3] and pain interference [item 9a]) and pain medication usage (Arm A and Arm B) and injection site pain (Arm B only) will also be captured using an evening daily diary (Table 2). Preference for route of administration (Arm A and Arm B) will be evaluated using a patient preference questionnaire (Appendix 14).

A blood sample for DNA extraction (ie, Retained Research Sample for Genetics) will be collected as outlined in the Table 2, unless prohibited by local regulations, IRBs/ECs. Serial ctDNA blood and tumor samples will be collected as outlined in Table 2.
Molecular profiling will be used to assess the association between breast tumor genomic alterations and tumor sensitivity/resistance to ARV-471.

An E-DMC will be established to review aggregate safety data to monitor safety and tolerability by treatment arm. The roles and responsibilities of the E-DMC are described in a separate charter.

A Global Steering Committee will be established at the program level for ARV-471. It will be responsible for providing scientific advice and medical input on the ongoing and future clinical development plans for ARV-471 in ER(+) breast cancer, including for this study.

Participants discontinuing the active treatment phase will enter a Post-treatment Follow-up period (Section 7.1.1). After completion of Safety Follow-up as per Section 7.1.1.1, the participant enters in the Survival Follow-up (See Section 7.1.1.2) during which survival and information on administration of any new anticancer therapy will be collected every 3 months from the EOT visit until one of the reasons for discontinuation from the study is met (as reported in Section 7.2).

This study is designed to test the PFS superiority of ARV-471 compared to fulvestrant in 1) all randomized participants, and 2) participants with ESR1 mutation.

It is anticipated that the final PFS analysis will occur at approximately 310 PFS events in all participants population and approximately 165 PFS events in the ESR1 *mutant* subgroup population. The final OS analysis will occur at approximately 194 OS events in the ESR1 mutant population and 396 OS events in the all participants population.

4.2. Scientific Rationale for Study Design

In nonclinical studies, ARV-471 has demonstrated robust ER degradation, superior activity against clinically relevant ER mutated forms (eg, Y537S and D538G), and improved TGI as single agent compared to fulvestrant in ER wild type and ESR1 *mutant* patient-derived xenograft models. In the FIH study, ARV-471 administered orally as single agent appears to be safe and well tolerated across total daily doses of 30 mg to 700 mg with preliminary evidence of efficacy in participants pretreated with CDK4/6 inhibitor plus endocrine therapy. These results support the hypothesis that ARV-471 may represent an important therapeutic approach in participants with ER(+)/HER2(-) advanced breast disease.

For further details, refer to Section 2.1, Section 2.2, Section 2.3 and ARV-471 IB.

4.2.1. Patient Input Into Design

Patient Insight surveys have been conducted in several countries via interviews through a third party. The team gathered qualitative insights to develop a deeper understanding of the breast cancer patient journey, uncover their views on clinical trials and options on certain aspects of the protocol assessments. No significant findings preventing study participation in the study design and Schedule of activities have been identified.

4.2.2. Diversity of Study Population

The diversity strategy will include high performing sites with the potential to support the recruitment of diverse and under-represented populations in the US. The strategy to ensure diversity includes:

- Use of county level census data in the US to help drive the site selection process and the selection of new/diverse investigators.

- Recognition that the presentation of aBC varies by gender, age, race, and geographic location.
- Inclusion of diversity in the steering committee and as principal investigators: leverage strong HCP networking across Black/African American and Hispanic/Latino(a)/Spanish participants, seeking sites that provide clinical care consistent with the known distribution of breast cancer in these populations.
- Site Support: site-level training on clinical study diversity – helping investigators and site staff to be actively more inclusive and think differently to enroll more diverse patients in studies.
- Portfolio level breast cancer education plan to community advocacy groups and breast cancer social media sites will drive potential patients to the site.

4.2.3. Choice of Contraception/Barrier Requirements

ARV-471 is known to cause reversible degenerative changes in the reproductive system organs of female rats and dogs and male dogs, which may be regarded as potential safety risks for women and men, and which are considered related to the pharmacologic activity of ARV-471. Therefore, there is a potential risk of male and female infertility. Studies to evaluate the effect of ARV-471 in pregnant women have not been conducted. However, based on mechanism of action, ARV-471 may cause fetal harm when administered to the pregnant woman.

Fulvestrant has been shown to cross the placenta after single intramuscular doses in rat and rabbit. Studies in animals have shown reproductive toxicity including an increased incidence of fetal abnormalities and deaths.

Contraception is required in male and WOCBP participants as per Table 2 and Appendix 4 in both Arms.

Refer to Faslodex EU SmPC for fulvestrant contraception requirements. Consultation with the sponsor medical monitor should be considered as needed, e.g. for male participants.

4.2.4. Collection of Retained Research Samples

Retained Research Samples will be collected and stored, as allowed per local regulations, IRBs and ECs, for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

4.3.1. ARV-471

In the FIH ARV-471-mBC-101 study, ARV-471 monotherapy was safe and well tolerated across total daily doses of 30 mg to 700 mg, without DLTs observed in the Part A dose escalation. The 200 and 500 mg daily doses were selected as RP2Ds and are currently being evaluated in the Part B monotherapy dose expansion portion of ARV 471-mBC-101.

Nonclinical data in MCF7 tumor-bearing mice showed dose-dependent tumor growth inhibition at doses of 3, 10 and 30 mg/kg with $\geqslant$ 94% estrogen receptor degradation in

tumors at all 3 doses (ARV-471 IB). This suggests that doses/exposures required for maximal anti-tumor activity are higher than those required for maximal ER degradation. Therefore, the nonclinical exposure threshold for maximal efficacy was targeted for RP2D dose selection. Based on the desire to maintain clinical exposures of ARV-471 above this threshold in the majority of patients and the lack of notable differences in safety across the doses evaluated in the Part A monotherapy dose escalation, 200 mg QD was selected as the lower dose for the Part B dose expansion. The dose of 500 mg QD was selected as the higher dose option in the expansion because exposure was mostly non-overlapping between 500 mg and 200 mg and exposures had been observed to plateau above 500 mg.

ARV-471 demonstrates a dose-dependent increase in ARV-471 exposure up to 500 mg with no notable differences in safety, ER degradation, or efficacy (as measured by clinical benefit response) observations across this dose range. An apparent higher risk for potential QTc prolongation was observed at 500 mg QD, supported by concentration QTc modelling and observed data from Parts A and B.

Data as of 06 June 2022 demonstrates that

- No meaningful differences in overall safety, such as treatment-related AEs, adverse events leading to discontinuations, or dose interruptions were noted, except for an apparent higher risk of potential QTc prolongation at 500 mg QD. Dose reductions occurred only at the 500 mg QD dose in Part B.

- No clear differences are observed in efficacy (by CBR) and no significant dose-response relationship is seen between the 200 mg and 500 mg daily doses in a heavily pretreated population.

Based on the totality of biologic evidence including clinical efficacy, safety, PK , PD, and nonclinical data, the 200 mg QD dose was selected as the RP3D for our proposed monotherapy Phase 3 studies (Arvinas, 2022).

4.3.2. Fulvestrant

For this device, the term “dose” refers to 500 mg (unit dose strength is 250 mg/5 mL) (Table 4) as per label.

4.4. End of Study Definition

The end of the study is defined when the approximate number of events required for final OS analysis is achieved

For information on continuation of the study treatment after the end of study, refer to Section 6.7.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a

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

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

5.1. Inclusion Criteria

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

Age and Sex:
1. Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening. a. Female participants under 60 years of age, with cessation of regular menses for 12 consecutive months and with no other alternative medical cause, must have a FSH level within the post-menopausal level, as per local laboratory reference range. b. Pre/ peri-menopausal female and male participants must agree to initiate or continue to use an LHRH agonist as per Table 2 and Section 6.9.1. c. WOCBP female and male participants must agree to use contraception. Refer to Appendix 4 for further details.
Disease Characteristics:
2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Histological or cytological confirmation of breast cancer with evidence of locoregional recurrent or metastatic disease which is not amenable to surgical resection or radiation therapy with curative intent. a. Documented ER(+) tumor, defined as ER(+) ≥10% stained cells by an assay consistent with local standards, on the most recent tumor biopsy, ie, at diagnosis of recurrence or metastatic disease (Allison et al, 2020). The sole exception is those participants with bone only disease and participants in whom the collection of a biopsy is clinically contraindicated, for whom ER(+) using archival tissue at initial diagnosis is acceptable.

b. Documented HER2(-) tumor by either IHC or *in-situ* hybridization per ASCO/CAP guidelines (Wolff et al, 2018)on the most recent tumor biopsy and as per above in inclusion criterion a. c. Participants who have bilateral breast cancers which are both ER(+)/HER2(-) are eligible. d. Participants must provide a blood sample AND a tumor sample collected at the time of diagnosis of locoregional recurrent or metastatic disease. If not available, a de novo biopsy is required unless the participant has bone only disease or in whom the collection of a biopsy is clinically contraindicated. In these cases, an archival tumor tissue at initial diagnosis is acceptable. Refer to Section 8.7.1 for details.
4. Prior therapies for locoregional recurrent or metastatic disease must fulfill all the following criteria: *Note:* Progression during or within 12 months from the end of adjuvant therapy is counted as a line of therapy in advanced/metastatic setting a. One line of CDK4/6 inhibitor therapy in combination with ET. Only one line of CDK4/6 inhibitor is allowed in any setting. b. ≤1 endocrine therapy in addition to CDK4/6 inhibitor with ET. c. Most recent endocrine treatment duration must have been given for ≥6 months prior to disease progression. This may be the endocrine treatment component of the CDK4/6 inhibitor line of therapy. d. Radiological progression during or after the last line of therapy
5. At least one measurable lesion as defined by RECIST version 1.1. Bone only disease: participants with only non-measurable disease are eligible. Refer to Section 8.2.1.
Other Inclusion criteria:
6. ECOG PS ≤ 1

5.2. Exclusion Criteria

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

Medical Conditions:
1. History of any other solid tumor malignancies within the past three years, except for the following: (1) adequately treated basal or squamous cell carcinoma of the skin; (2) curatively treated *in situ* carcinoma of the cervix. For all other solid tumors, must have been curatively treated and with no evidence of disease for >3 years. Participants with inflammatory breast cancer are excluded.
2. Participants with newly diagnosed brain metastasis or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Participants with a history of CNS metastases or cord compression are eligible if they have been definitively treated (e.g., radiotherapy, stereotactic surgery) and clinically stable (including participants with residual CNS symptoms/deficits) off enzyme-inducing anticonvulsants and steroids for at least 14 days prior to randomization.
3. Major surgery or radiotherapy or prior endocrine therapy, CDK4/6 inhibitor, or other anticancer treatments within 14 days of randomization (28 days or 5 half-lives, whichever is shorter, for anticancer therapy containing an antibody- based agent, approved or investigational). Participants who received prior radiotherapy to ≥ 25% of bone marrow are not eligible independent of when it was received (Appendix 12).
4. Participants in visceral crisis at risk of immediately life-threatening complications in the short term, including participants with massive uncontrolled effusions (pleural, pericardial, and peritoneal), pulmonary lymphangitis, or liver involvement > 50%.
5. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as: • Any of the following *in the previous 6 months*: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease, congenital long QT syndrome, Torsade de Pointes, clinically important arrhythmias, left anterior hemiblock (bifascicular block), ongoing cardiac dysrhythmias of NCI-CTCAE Grade ≥2, atrial fibrillation of any grade. • Participants with cardiac rhythm device/ pacemaker (QTc Sub-study). For all the other participants with cardiac rhythm device/pacemaker eligibility must be discussed in detail with the sponsor medical monitor. • QTcF interval >470 msec on screening ECG.

• Symptomatic cardiac valve disease. Participants with mitral valve prolapse which is asymptomatic or not associated with clinically significant sequelae (eg, mitral regurgitation) are eligible.
6. Refractory nausea and vomiting, chronic GI disease, GI ulcer, GI bleeding, inability to swallow the formulated product, or previous significant gastric (total or partial) or bowel resection that would preclude adequate absorption of study drug.
7. 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.
Prior/Concomitant Therapy:
8. Concurrent administration of medications, food or herb supplements that are strong inhibitors and inducers of CYP3A and drugs known to predispose to Torsade de Pointes or QT interval prolongation (see Section 6.9 and Appendix 10 for the list of prohibited medications). Prior use of strong CYP3A inhibitors must be stopped 7 days and strong inducers of CYP3A must be stopped 14 days before randomization.
9. Prior treatment with: a) ARV-471, fulvestrant, elacestrant, mTOR, PI3K, AKT pathway inhibitors, PARP inhibitor, other investigational agents (including novel endocrine therapy any SERDs, SERCAs, CERANs) for any setting b) prior chemotherapy for advanced/metastatic disease Participation in other studies involving investigational drug(s) within 28 days prior to randomization. If in the FU Phase, the participant is eligible provided at least 5 half-lives have elapsed from the last dose.
10. Any unresolved toxicities from prior surgeries or therapies Grade >1 (Grade > 2 for peripheral neuropathy) by NCI-CTCAE Version 5.0 at the time of randomization except for alopecia.
Diagnostic Assessments:
11. Hepatic dysfunction defined as: • Total bilirubin >1.5 x ULN unless the participant has documented Gilbert's syndrome (in this case total bilirubin ≥3 x ULN); • AST and ALT >3 x ULN; >5.0 x ULN if liver metastases present; • Alkaline phosphatase >2.5 x ULN; >5 x ULN in case of bone metastasis.

• aPTT >1.25 x ULN and INR >1.25 unless the participant is receiving anticoagulation, then aPTT and INR should be within the therapeutic range of the intended use.
12. Hematologic abnormalities defined as: • ANC <1500/mm^3 or <1.5 x 10^9/L; • Platelets <100,000/mm^3 or < 100 x10^9/L; • Hemoglobin <9 g/dL. One transfusion allowed ≤2 weeks before randomization.
13. Renal impairment defined as an eGFR <45 mL/min/1.73m^2 as calculated using the 2021 CKD-EPI Equations as outlined in Appendix 7.
14. Known active infection including SARS-CoV-2 infection, HBV, HCV, and HIV or AIDS-related illness (screening for chronic conditions is not required).
Other Exclusion Criteria:
15. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

Restrictions regarding lifestyle for study eligibility and/or participation are reported in the Sections below. The food requirement for ARV-471 intake is detailed in Section 5.3.2.

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is using an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. As applicable, at time points indicated in Table 2, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

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

as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

Participants must be instructed to take ARV-471 with food. Participants should be instructed to take ARV-471 at approximately the same time preferably in the morning.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, have completed the pre-screening period, but are not subsequently randomized 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 screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once. Rescreened participants must be assigned a unique participant number that is different from the participant number used for the initial screening.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to ARV-471, and the drug for the control arm refers to fulvestrant.

6.1. Study Intervention(s) Administered

Table 4. Study Interventions Administered

Intervention Name	ARV-471 (PF-07850327)	Fulvestrant
ARM Name	A (Investigational)	B (Comparator)
Type	Drug	Drug
Intervention Name	ARV-471	Fulvestrant
Dose Formulation	Tablet	Solution for IM injection
Unit Dose Strength(s)	100 mg	250 mg/5 mL
Dosage Level(s)	200 mg	500 mg
Route of Administration	Oral	IM
Use	Experimental	Active comparator

Table 4. Study Interventions Administered

IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Please refer to the IPM.	Provided centrally by the sponsor. Please refer to the IPM.
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 local regulations.	Study intervention will be supplied as two 5 mL glass (Type 1) prefilled-syringe, each containing 250 mg / 5 mL of fulvestrant for IM injection. Each carton will be labeled per local regulations.
Current/Former Names or Aliases	ARV-471 (PF-07850327)	Fulvestrant, Faslodex®

Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments, including temperature monitoring data, and the chain of custody of the study intervention must be kept in the participant's source documents/medical records. Fulvestrant preparation and administration must be performed by a physician, registered nurse, or other qualified health care provider and documented in the participant's source documents/medical records. Please refer to IPM for dosing instructions.

6.1.1. Administration

Participants in Arm A will receive ARV-471, and participants in Arm B will receive fulvestrant. Study drugs will be provided open-label. ARV-471 will be administered in tablet form and be self-administered. Fulvestrant will be administered intramuscularly by a physician, registered nurse, or other qualified health care provider. Participants must receive study intervention within 3 days after randomization.

Refer to the IPM for detailed administration instructions for all the study drugs administered in this study.

6.1.1.1. ARV-471

ARV-471 will be administered open-label as 100 mg tablets to participants in Arm A (Table 5). ARV-471 will be administered orally, once daily on Days 1-28 of each 28-day cycle according to Table 2. Recommended dose modifications for toxicity related to study intervention are presented in Table 6 and Table 7.

Participants must be instructed to take ARV-471 with food. Participants should be instructed to take ARV-471 at approximately the same time preferably in the morning, and to not take more than the pre-specified dose at any time. Participants will swallow ARV-471 whole, and

not manipulate or chew ARV-471 prior to swallowing. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

On visit days, participants must be instructed to not take their ARV-471 dose and to wait to take ARV-471 dose until they have completed their pre-dose study assessments as per Table 2 and Table 3. On these days, ARV-471 doses should be taken under the supervision of the study personnel.

Each participant treated with ARV-471 will be given a dosing diary and should be instructed to record the daily administration of the study drug. Study personnel must ensure that participants clearly understand the directions for self-medication. Participants will be given a sufficient supply of study drug for administration on each dosing day until their next scheduled study visit. Participants should be instructed to maintain ARV-471 in the bottles provided throughout the course of dosing. Unused drug and/or empty bottles should be returned to the site/ provided to the vendor (in case of home health visit) at the next study visit. Returned unused study intervention MUST NOT be re-dispensed to a participant.

If a participant misses a day of treatment, they must be instructed not to double-up or "make up the dose", but to resume dosing on the next day of the dosing cycle as prescribed.
If a participant vomits any time after taking a dose, they must be instructed not to "make it up", but to resume dosing on the next day of the dosing cycle as prescribed. If a participant inadvertently takes 1 extra dose during a single dosing day, the participant should not take the next dose of study intervention for the next day (see Section 6.8).

6.1.1.2. Fulvestrant

Fulvestrant preparation and administration will be performed by a physician, registered nurse, or other qualified health care provider. Refer to the IPM for detailed administration instructions.

Fulvestrant should be administered intramuscularly on Days 1 and 15 (±2) of Cycle 1. Then from cycle ≥2, on Day 1 of each cycle.

Dose reductions for fulvestrant are not permitted for any reason.

6.1.2. Medical Devices

Fulvestrant, the open label comparator detailed in Table 4, will be provided as a prefilled syringe and, in which case should be considered a medical device. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take home study intervention.

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator/vendor (in case of home health visit) by the participant. **Returned study intervention must not be redispensed to the participants.**

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. 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 IPM.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention for Arm A and Arm B using the IRT system via unique container numbers on the bottles or prefilled syringe and provided in sufficient quantities according to the dosing schedule outlined in Table 2. A second staff member will verify the dispensing.

Bottles (ARV-471):

The participant/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing and return to the site /provide to the vendor (in case of home health visit) the bottle at the next study visit.

Pre-Filled Syringe (fulvestrant):

Fulvestrant is supplied as two 5 mL glass (Type 1) single-dose pre-filled syringes, each containing 250 mg/5 mL of fulvestrant solution for IM injection and fitted with a tamper evident closure. Refer to IPM for instructions and steps necessary for drug preparation and administration. Drug preparation and administration will be performed by a physician, registered nurse or other qualified health care provider.

6.3. Assignment to Study Intervention

This is an open-label, Phase 3 study; however, the specific study intervention dispensed to each participant will be assigned using an IRT. Participants will be randomized based on a 1:1 randomization allocation ratio to receive either ARV-471 (Arm A) or fulvestrant (Arm B), provided they have satisfied all participant selection criteria.

Eligible participants will be stratified by:

- ESR1 mutational status (*Mutant*, Yes/No)
  In the event the ESR1 test is not informative (ie, test performed but the result is "unknown") the participant will be stratified as participant with *Mutant* "NO".

- Visceral disease: (Yes/No)
  Visceral refers to lung, liver, brain, pleural and peritoneal involvement.

Stratification factors should be carefully verified before randomization. Randomized participants cannot be de-randomized.

This stratified randomization will be centrally allocated using an IRT system (IWR).

The site will record the study intervention assignment on the applicable CRF, if required. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit or container number when study intervention is being supplied via the IRT system. The IRT system will provide a

confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study treatment must start within 3 days after a participant's randomization. Study intervention will be dispensed at the study visits summarized in Table 2.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

When participants self-administer study intervention at home compliance with ARV-471 will be assessed at each cycle, prior to the dispensing of study intervention for the next cycle Participants will receive a dosing diary to document self-administered dosing of study intervention in each cycle to include the dose of study intervention taken, the date of dosing, if any doses were missed and the reason for the missed dose.

Compliance will be assessed by a review of diary entries and/or direct questioning and/or counting returned tablets during the visits. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF and study staff will document their follow-up with the participant in the source records when they discover compliance discrepancies. Participants must be instructed to return or to provide to the vendor (in case of home health visits) all bottles of study intervention, as well as the completed participant dosing diary at each cycle for drug compliance. The number of remaining tablets will be documented in the source document. In absence of toxicity requiring dose modifications (ie, reduction, interruption and/or delay), each study participant is considered underdosed if less than 80% of the prescribed dose for the given cycle has been administered. 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. Study intervention start and stop dates, including dates for intervention interruptions and/or dose reductions, will also be recorded in the CRF.

Fulvestrant will be administered by a physician, registered nurse, or other qualified health care provider in accordance with the IPM. Fulvestrant administration will be documented on the corresponding study drug administration CRF. The date administered will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study staff other than the person administering the study intervention. Any dose delay or dose skipped (only at C1D15) for reasons other than treatment related toxicity will be considered as non-compliance.

6.6. Dose Modification

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment toxicity, administration of study intervention

may need to be modified based on the toxicity observed. 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.

6.6.1. Fulvestrant

No dose reduction for fulvestrant is permitted. In case of fulvestrant-related toxicities, C1D15 may be delayed as per the investigator's best medical judgment, but for no more than 7 days. If more than a 7 day delay is required then the C1D15 dose should be skipped and C2D1 will be performed as per Table 2. If C1D15 is delayed, C2D1 fulvestrant injection should be performed at least 14 days (+/- 2 days) from the last dose.

Dosing from cycle ≥2 can be delayed for fulvestrant-related toxicities as per the investigator's best medical judgment.

See Faslodex EU SmPC of fulvestrant treatment details.

Following treatment delay, the day when treatment is restarted will be counted as Day 1 of the next cycle. Procedures required as per Table 2 and Table 3 on Day 1 of the given cycle will be performed when study treatment is resumed. In the event of a treatment delay lasting >28 days, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the sponsor medical monitor. See Faslodex EU SmPC for fulvestrant treatment details.

6.6.2. ARV-471

Dose modifications may occur in 1 of 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

6.6.2.1. ARV-471 Dose Reductions

Following dosing interruption or cycle delay due to toxicity, ARV-471 study intervention dose may need to be reduced when treatment is resumed.

No specific dose modifications are recommended for Grade 1 or 2 treatment-related toxicity. However, investigators should always manage 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.

Dose reduction of ARV-471 by 1 dose level (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 enter the Follow-up phase. All dose modifications must be clearly documented in the participant's source notes and CRF.

Table 5. ARV-471 Dose Modification Levels for Adverse Reactions

Dose Level	Dose	Administration of Dose
Starting Dose	200 mg daily	Two 100 mg tablets once daily
-1	100 mg daily*	One 100 mg tablet once daily

*ARV-471 dose de-escalation below 100 mg/day is not allowed.

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at that dose level.

However, if the participant has demonstrated significant benefit, dose re-escalation of ARV-471 may be considered after consultation with the sponsor medical monitor, if the AE was rapidly reversible, and re-escalation is not expected to pose a significant risk to the participant.

Depending on the nature of the toxicity and the rapidity of recovery following dose interruption, resumption of the same dose may be considered after a related Grade 3 AE.

6.6.2.2. Recommended ARV-471 Dose Modifications

Recommended dose modifications for study intervention are described in Table 6.

Table 6. Recommended Dose Modifications for ARV-471 -Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	Continue at the same dose level. Refer to Table 7 for QTc prolongation management.	Withhold dose until toxicity is Grade ≤1, (Grade ≤2 if not considered a safety risk for the participant). Then resume treatment at the same dose level or at the next lower dose level at the discretion of the investigator*. *Exceptions:* • Laboratory values that do not have any clinical correlate (eg, amylase or lipase abnormality	Withhold dose until toxicity is Grade ≤1. Then resume treatment at the next lower dose level or discontinue at the discretion of the investigator. *Exceptions:* Laboratory values that do not have any clinical correlate. (eg, amylase or lipase abnormality that is not associated with

Table 6. Recommended Dose Modifications for ARV-471 -Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
			that is not associated with symptoms or clinical manifestations of pancreatitis). Refer to Table 7 for QTc prolongation management.	symptoms or clinical manifestations of pancreatitis). Refer to Table 7 for QTc prolongation management.
Hematologic**	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2. Then resume treatment at the same dose level.	Withhold dose until toxicity is Grade ≤2. Then resume treatment at the next lower dose level.

* Grade 3 fatigue lasting <7 days, grade 3 nausea/vomiting/diarrhea lasting <72 hours in the absence of maximal medical therapy do not require dose reduction.
**Recommendation applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, eg, opportunistic infections).

6.6.2.3. ARV-471/QTc prolongation management

In the event of QTc prolongation, possible alternative reversible causes such as serum electrolytes abnormalities or potential usage of concomitant medications with the potential to prolong the QTc interval should be evaluated.

If such reversible causes are identified, they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation of concomitant medications known to prolong the QT interval).

No specific dose modifications are recommended for Grade 1 treatment-related toxicity.

Recommended dose modifications in the event of QTc prolongation are provided in Table 7.

Table 7. Recommended ARV-471 Dose Modification in the event of QTc Prolongation

	Grade 2 QTc prolongation (Average QTc 481 - 500 ms)	**Grade 3 QTc prolongation (Average QTc ≥ 501 ms; or >60 ms change from baseline)**	**Grade 4 QTc Prolongation (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)**
Reversible cause identified	Treat reversible cause; Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec. Continue at the same dose level[1]	Treat reversible cause; If QTc ≥501 msec withhold treatment until recovery to ≤ Grade 2; Then resume treatment at the same dose level; Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec. If QTc >60 msec change from baseline but QTc <501 ms continue at the same dose level with more frequent ECG monitoring until QTc ≤480 msec AND ≤ 60 msec change from baseline.	Treat reversible cause; Permanently discontinue
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec. Continue at the same dose level[1]	If QTc ≥501 msec withhold treatment until recovery to ≤ Grade 2; Then resume treatment at the LOWER dose level[2]; Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec. If the increase of QTc is >60 ms from baseline but QTc <501 msec continue at the LOWER dose level[2] with more frequent ECG monitoring until QTc ≤480 msec AND ≤ 60 msec change from baseline.	Permanently discontinue

Table 7. Recommended ARV-471 Dose Modification in the event of QTc Prolongation

	Grade 2 QTc prolongation (Average QTc 481 - 500 ms)	Grade 3 QTc prolongation (Average QTc ≥ 501 ms; or >60 ms change from baseline)	Grade 4 QTc Prolongation (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)

1 If the QTc remains above 480 msec for more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose modification and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the emerging safety data from ARV-471 trials and the investigator's best medical judgment.

2 If the Grade 3 QTc prolongation recurs after one dose reduction, discontinuation should be discussed with study medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from ARV-471 trials and the investigator's best medical judgment.

6.6.2.4. ARV-471 Dosing Interruptions

With respect to ARV-471 study intervention, participants experiencing the following AEs should have their treatment interrupted as reported in Table 6 and Table 7.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Section 6.6.2.5.

Doses may be held up to 28 days until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the participant missing all subsequent planned doses within that same cycle or even to a delay of the initiation of the subsequent cycle. If the AE that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 6.6.2.2 and Section 6.6.2.3 (See Table 6 and Table 7), unless expressly agreed otherwise following discussion between the investigator and the sponsor medical monitor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >28 days, treatment resumption will be decided in consultation with the sponsor/medical monitor.

6.6.2.5. ARV-471 Dose Delays

Re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC ≥1000/mm^3.

- Platelet count ≥50,000/mm^3.
- Grade ≥3 nonhematologic toxicities have returned to Grade ≤1 severity (or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the participant). See exception in Table 6.
- QTc <501 msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, ECG should be monitored more frequently as per the investigator's best medical judgement until QTc ≤ 480 msec.

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 28 days of treatment interruption, ARV-471 may be resumed. Refer to Table 6 and Table 7 for AEs requiring dose reduction at the time of treatment resumption.

If participants require interruption of ARV-471 for more than 28 days at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the sponsor medical monitor.

If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle. Procedures required as per Table 2 and Table 3 on Day 1 of the given cycle will be performed when study treatment is resumed.

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

No intervention will be provided per protocol to study participants beyond the end of the study. Availability of study drugs following closure of the study through expanded access/continued use mechanism if the investigator and participant desire to continue treatment would be at the discretion of the sponsor and subject to local conditions and regulations.

6.8. Treatment of Overdose

For this study, any dose of ARV-471 or fulvestrant greater than the prescribed dose assigned at Cycle 1 day 1 as per Section 6.1 will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose; treatment should be supportive.

In the event of an overdose, the investigator should:

- Contact the study medical monitor within 24 hours.

- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

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

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

6.9. Prior and Concomitant Therapy

Participants must be instructed not to take any additional medications (over the counter or other products) during the study without prior consultation with the investigator. Any medications including herbal supplements, vitamins, or treatment (as reported in the sections below) taken by the participant from signature of the informed consent and up to 28 days following the last dose of investigational product must be recorded on the CRF along with:

- Reason for use.

- Dates of administration including start and end dates.

- Dosage information including dose and frequency.

The sponsor Medical Monitor or designee should be contacted if there are any questions regarding concomitant or prior therapy.
Concomitant treatment considered necessary for the participant's well-being may be given at the discretion of the investigator. All concomitant treatments, blood products, as well as non-drug interventions (eg, paracentesis) received by participants from signature of the informed consent in the main study and up to 28 days following the last dose of investigational product must be recorded on the CRF.

6.9.1. Luteinizing Hormone-Releasing Hormone Agonist

Ovarian/testicular suppression therapy with an LHRH agonist (eg, goserelin or leuprolide acetate or equivalent agents) must be administered in pre/peri-menopausal female and male participants, starting on Cycle 1 Day 1 (if not already on treatment) and then administered every 28 days/3 months (depending on the LHRH formulation) irrespectively of cycle duration up to 28 days after the last dose of study intervention (Table 2).

Participants already on treatment with the 28-day/3-month LHRH formulation can continue it for the duration of the trial. Formulations given at intervals >3 months are NOT allowed. The Investigator will determine and supply the appropriate LHRH agonist locally approved for use in BC considering any potential DDI based on the product prescribing information. If required by local regulations, LHRH may be provided by the Sponsor if available to source

in-country. If LHRH agonist is administered at home, the administration details will be collected in a diary. The completed diary should be provided to the study personnel at every visit.
LHRH agonist treatment continuation during the survival FU will be at the discretion of the PI in both arms.

6.9.2. Prohibited Inhibitors/Inducers

The concurrent use of the following medications, food or herb supplements is prohibited throughout the duration of the active treatment phase:

Arm A

- **Strong CYP3A inhibitors/inducers**: CYP3A4 is involved in ARV-471 metabolism based on in vitro assays. Co-administration with drugs that are strong CYP3A inhibitors and inducers may change the plasma concentrations of ARV-471 in humans. Refer to Appendix 10 for examples of drugs that are strong CYP3A inhibitors/inducers.

Arm B

- No DDI is expected by the concomitant use with fulvestrant. Refer to Faslodex EU SmPC.

6.9.3. Other Prohibited and/or Anti-Cancer or Experimental Drugs, or Procedures

The following treatments are also prohibited throughout the duration of the active treatment phase **in both Arms**:

- **Anticancer agents:** No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than the initiated treatment by the investigator will be permitted during the active treatment phase. No switching will be permitted. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on study.

- **Hormone replacement therapy**, topical estrogens (including any intravaginal preparations), megestrol acetate and selective estrogen receptor modulators (e.g., raloxifene).

- **Drugs known to predispose to Torsade de Pointes or to QT interval prolongation**: refer to Appendix 10 for a list of drugs known.
Exception: sevoflurane, azithromycin, ondansetron, chloroquine may be used **with caution** during the active treatment for all the participants with the exception of the participants in the QTc sub-study in Arm A for whom the use is prohibited during Cycles 1, 2 and 3.

6.9.4. Concomitant Treatments to be used with caution or not recommended

The following treatments are to be used **with caution** throughout the duration of the active treatment phase:

Arm A only:

- **P-gp sensitive substrates**: based on in vitro data ARV-471 may inhibit P-gp substrates. Drugs that are P-gp sensitive substrates should be used with caution as ARV-471 may increase the drug exposure. Consult the respective local product label of the P-gp substrate before use. Refer to Appendix 10 for examples of drugs that are sensitive substrates of P-gp.

- **H2 receptor antagonists** (eg, cimetidine, famotidine) or **antacids** (eg, aluminum hydroxide, calcium carbonate, bismuth subsalicylate) 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 H2 receptor antagonists. Alternatively, H2 receptor antagonists or antacids can be administered anytime when ARV-471 is taken with a moderate-fat meal (400-800 calories, approximately 35% fat).

The following treatments are **NOT recommended** throughout the duration of the active treatment phase in:

Arm A only:

- PPIs: 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 drug intake with a moderate-fat meal (400-800 calories, approximately 35% fat) is recommended. Refer to Appendix 10 for examples of drugs that are PPIs.

Both Arms:

- Herbal medicine: use of herbal medicine.

Consider, whenever possible, to replace the concomitant treatments to be used with caution or not recommended with other drugs with the same indication for use. If one of the treatments to be used with caution or not recommended is deemed necessary, consultation and agreement with the sponsor medical monitor is encouraged prior to treatment initiation.

6.9.5. 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.

Participants should receive appropriate supportive care measures throughout duration of the active treatment phase as deemed necessary by the treating investigator including but not limited to the items outlined below:

- **Standard therapies** for preexisting medical conditions, medical and/or surgical complications, and palliation. Any medication intended solely for supportive care (e.g., analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion.
- **Bisphosphonates and receptor activator of nuclear factor kappa B ligand** inhibitors for the treatment of osteoporosis or management of existing bone metastases may be continued for participants who have been receiving them at a stable dose for at least 2 weeks prior to randomization. However, the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of participant from the active treatment phase unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the subject's source documentation.
- **Vaccines** locally approved vaccinations and booster doses are allowed, including Influenza and SARS-CoV-2 as appropriate.
- **Transfusion**: RBC and PLT transfusion may be used as per Investigator's discretion
- **Anti-infectives** may also be used at the investigator's discretion. Before administration verify any potential drug-drug interaction with the study treatments as per Appendix 10.
- **Anticoagulant's use**:
  Arm A only: Participants who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, warfarin or other warfarin derivatives or other oral anticoagulants (eg, direct Xa inhibitors) may be allowed. When using oral anticoagulants, close monitoring for signs of bleeding is recommended. Consult the product prescribing information for the appropriate coagulation test to be used for monitoring, as required. Refer to Appendix 10 for potential DDI with P-gp sensitive substrates.
  Arm B: refer to the Faslodex EU SmPC for fulvestrant for anticoagulant's use.

6.9.6. Hematopoietic Growth Factors

Hematopoietic growth factors (eg, GCSF and GMCSF) may be used as indicated by the ASCO guidelines (Smith et al, 2015).

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia. For those countries where the indication and dosage of GCSF compounds may differ from ASCO guidelines, refer to the local product prescribing information or follow the country's clinical practice.

6.9.7. Antidiarrheal, Antiemetic Therapy

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

Antidiarrheal: All participants who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Anti-diarrheal agents should be administered as needed.

Antiemetic Therapy: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.

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 drug-drug interaction and assuming the drug is not included in the Concomitant Therapy section (Section 6.9).

6.9.8. Corticosteroids

Chronic immune suppressive therapies, including systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. Steroids given as hormonal replacement (prednisone ⩽ 10 mg/day or equivalents) is allowed.

Acute emergency administration, topical applications, inhaled sprays, eye drops, local injections of corticosteroids or as premedication prior to contrast media administration as per local guidelines is allowed.

6.9.9. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected DDI and assuming the drug is not included in the Concomitant Therapy section (Section 6.9). Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

6.9.10. Concurrent Surgery and Radiotherapy

Any concurrent radiotherapy (excluding palliative radiotherapy as per specifications below) or cancer related surgery are prohibited throughout the duration of the active treatment phase of the study. Participants requiring any of these procedures will be discontinued from the active treatment phase and will enter the follow-up phase.

Caution is advised for any participant undergoing surgical procedures during the study. The appropriate interval of time between surgery and ARV-471 administration required to minimize the risk of impaired wound healing and bleeding has not been determined. It is recommended to stop ARV-471 administration at least 7 days prior to surgery.

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 is permitted for the treatment of painful bony lesions providing the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. ARV-471 treatment is recommended to be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment after recovery of any radiotherapy associated signs and symptoms.

For participants with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (eg, lesions at risk for spontaneous micro-fractures or painful lesions). Information related to the administration of palliative radiotherapy (eg date and site of radiotherapy) should be recorded on the appropriate CRFs.

No contraindication is reported for concomitant surgery and radiotherapy in respect to the use of fulvestrant. Refer to Faslodex EU SmPC.

6.9.11. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with ARV-471 or fulvestrant; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Objective disease progression assessed by Investigator; however, participants with disease progression as per RECIST v1.1 who are continuing to derive clinical benefit from the study intervention (ie, positive benefit/risk assessment as assessed by investigator), will be eligible to continue study intervention. See Section 8.2.1.1 for details;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to followup;

- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety and survival. See Table 2 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.

7.1.1. Post-treatment Follow-up

Participants discontinuing the Active Treatment Phase will enter to the Post-treatment Follow-up period, which comprises Safety and Survival Follow-up Periods (see Table 2 for required assessments).

7.1.1.1. Safety Follow-up

At least 28 calendar days, and no more than 35 calendar days after discontinuation of study intervention or prior initiation of any new anticancer therapy whichever comes first, participants will undergo the safety FU assessments as reported in Table 2.
Any SAEs occurring during the 28-day from last dose must still be reported to Pfizer Safety irrespective of any intervening treatment. See Section 8.4.1 for details for AE/SAE reporting requirements.

7.1.1.2. Survival Follow-up

During the Survival Follow-up period, poststudy survival status (including all poststudy anticancer therapies) will be collected every 3 months after the EOT visit. Participants will be contacted (eg, telephone, email, site visits, family member contact) approximately every 3 months after the EOT visit for survival status and subsequent anticancer therapies (eg, start and stop dates, date of PD of the therapy), until death, withdrawal of consent, lost to follow-up, or end of study, whichever occurs first. On sponsor request, participants may be contacted for survival information (including all poststudy anticancer therapies), eg prior to each protocol-specified interim and final analysis. As permitted by local law, study site personnel may use public databases, perform an internet search, or review obituaries to determine date of death. Survival information should be recorded in the CRFs.

7.1.2. COVID-19

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. When the infection resolves, the participant may be considered for re-screening.

If a participant has COVID-19 during the active treatment phase, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided considering potential DDIs for any concomitant medication administered for treatment of SARS-CoV-2 infection (see Section 6.9). Study treatment should continue unless the investigator is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required. In case of temporary discontinuation, prior 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.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Withdrawal by participant.

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline 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 Table 2. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the Table 2, 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, tumor assessments by imaging as per Section 8.2.1) and obtained before signing of the ICD of the study may be utilized for screening purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in Table 2.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the

test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

The total blood sampling volume for individual participants in this study is approximately from minimum of 10 mL up to approximately 40 mL per study visit. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1.1. Pre-screening

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

Study procedures are summarized in Table 1.

Three mandatory whole blood samples (10 mL each) (only two samples for China) for ctDNA will be collected during pre-screening period as per Table 1. Available ESR1 results (with the exception of participants in China) may also be considered upon sponsor approval as per Table 1.

The samples will be collected as follows:

- All participants with the exception of China: The collection of the 3 samples is mandatory for all the participants and will be used either for ESR1 status evaluation or for retrospective ESR1 confirmation after randomization (only for the participants with an acceptable and approved prior ESR1 status result) and may also be used for the development of companion diagnostics. One of the 3 samples is to be processed into plasma at the study site as per Laboratory manual instructions. The other two whole blood samples will be sent directly to the laboratory identified for analysis. See Laboratory Manual.

- For participants in China: Two samples are mandatory from participants in China for ESR1 status evaluation. The remaining sample may also be used for the development of companion diagnostics. The sample may be also used for tumor molecular profile/ctDNA level and ctDNA burden if the participants are randomized in the trial. See Laboratory Manual.

ESR1 test will be performed using a NGS test that evaluates other genes in addition to ESR1 gene. The results of the other genes will not be collected in the CRF.

Some characteristics regarding the disease under study, demography and study procedure-related AEs will be also collected.

8.1.2. Baseline Procedures

Medical history will be recorded at screening for each participant. Medical history includes any signs, symptoms, and history not associated to the disease under study before informed consent signature.

Oncological history will be recorded at screening for each participant and includes additional disease characteristics, and all prior treatments including prior systemic therapies, radiation, and surgical procedures.

8.1.3. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points upon written confirmation from the sponsor. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing 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 (see the Table 2):

- 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 8.4.
- Review and record any new concomitant medications/treatment (eg, radiotherapy or surgery as per Section 6.9.10) or changes in concomitant medications/treatment since the last contact.
- Review laboratory tests and ECGs reports performed at alternative facilities, if applicable.
- Review LHRH compliance for pre/peri-menopausal female and male participants (Section 6.9.1) and contraception for WOCBP and males.
    - Review and record contraceptive method and results of pregnancy testing, (Section 8.3.5) as applicable. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- PRO assessment, as applicable (See Appendix 14)

Participants should be instructed to bring original reports of assessments performed in alternative facilities and diaries at the next visit.

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

8.1.4. Home Health Visits

A home health visit may be utilized to facilitate scheduled visits and will be allowed on a case-by-case basis. Confirmation from the sponsor will include which visits can be performed at home.

Home heath visits will be performed by a registered nurse/other qualified health care provider and the investigator or designee must be available for consultation. If required by local regulations home heath visits will be performed by the investigator or by a physician designee for specific assessments (e.g. fulvestrant intramuscular administration, physical examinations and collection of adverse events).

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 (see Table 2):

- Review and record study intervention(s), including compliance and missed doses; dispense dosing diary (if applicable)
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications/treatment (eg, radiotherapy or surgery as per Section 6.9.10) or changes in concomitant medications/treatment since the last contact.
- Collect local safety laboratory samples and review laboratory tests, perform and review ECGs, if applicable.
- Collect central laboratory samples, including ctDNA samples and PK samples, if applicable.
- Review LHRH compliance and provide diary, if applicable; administer LHRH (if applicable) for pre/peri-menopausal female and male participants (Section 6.9.1) and review contraception for WOCBP and males.
    - Review and record contraceptive method and perform pregnancy testing (Section 8.3.5) and review results, as applicable. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Perform physical examinations and collect vital signs
- Administer and provide PRO assessments, if applicable

Dispense/administer ARV-471 or fulvestrant; fulvestrant preparation and administration must be performed by a physician, registered nurse, or other qualified health care provider.

Tumor assessments (ie, all tumor scans, photographs, etc) must be performed at the site, unless otherwise agreed between the investigator and the sponsor (see Section 8.1.5).

8.1.5. Alternative Facilities

In the event that an in-person visit is not feasible at the site, the following may be performed at alternative facilities, approved by the investigator upon written notification from the sponsor, if allowed by local regulations (see Table 2):

- **Safety laboratory tests**. See Section 8.3.4.1.
- **ECGs.** See Section 8.3.3.1.
- **Tumor assessments** (ie, all tumor scans, photographs, etc.). See Section 8.2.1.4

8.2. Efficacy Assessments

8.2.1. Imaging Tumor Response Assessments

Timely and complete disease assessments in this study are critical. Imaging assessments are to be scheduled according to the calendar, starting from the randomization date as the reference date for all time-points regardless of treatment delays/interruptions and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is NOT permitted.

Radiographic imaging, for all known or suspected disease sites, is required at screening and during the active treatment phase using the **same** imaging techniques. The CT and MRI scans (including brain CT/MRI, if applicable) should be performed with contrast agents unless contraindicated for a medical reason. Premedication prior to contrast media administration as per local guidelines is allowed. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, CT of the chest should not be substituted by chest MRI even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow up bone lesion(s) it must be performed a few days before any treatment that may affect bone marrow cellularity (ie, G-CSF).

Screening tumor assessment will be carried out within 28-day period before randomization unless otherwise specified. Disease assessment for all participants at screening will include:

- Imaging assessments of chest, abdomen and pelvis (CAP), by computerized tomography (CT) or magnetic resonance imaging (MRI) mandatory.
- CT/MRI scan of any other sites of disease (including brain), as clinically indicated.
- Clinical assessment of superficial lesions, as clinically indicated.

- Bone scan (whole body), mandatory

Screening CT/MRI scans obtained per the participant's standard of care prior to the signature of the informed consent do not need to be repeated and are acceptable to use as baseline evaluations, (1) obtained within 28 days before randomization, (2) they were performed using the method requirements outlined in RECIST v1.1, (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given participant, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the participant's source notes.

Screening brain scan is only required if signs and symptoms suggest the presence of metastatic brain disease. Brain scans performed before the signing of informed consent as routine procedures (but within 6 weeks before randomization) do not need to be repeated and may be used as screening assessments as long as (1) tests were performed using the method requirements outlined in RECIST v1.1, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given participant, (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the participant's source notes. Post-baseline brain scans are required only if brain metastases are present at screening or in case new brain lesion/s is/are suspected.

Clinical assessment of superficial lesions will include assessment with caliper of all identified superficial metastatic lesions. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Screening bone scan is mandatory to detect bony sites of disease. Bone scans performed before the signing of informed consent as routine procedures (but within 12 weeks before randomization) do not need to be repeated and may be used as screening assessments as long as (1) tests were performed using the method requirements outlined in RECIST v1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given participant (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the participant's source notes. Any suspicious abnormalities (ie, hotspots) identified on the screening bone scans and on subsequent bone scans MUST be confirmed by X-ray, CT scan with bone windows or MRI. Bone lesion(s) identified at screening by bone scan can be further assessed at screening by CT with bone windows or MRI as per local practice and subsequently re-assessed on treatment by CT with bone windows or MRI (consistently with the technique used at screening) as per tumor assessment schedule (ie, every 8 weeks for the first 48 weeks from the date of randomization and then every 12 weeks thereafter). Areas that have received palliative radiotherapy cannot be used to assess response to study treatment.

All lesions identified at screening, measurable and/or non-measurable, must be recorded in the CRF and evaluated during the active treatment phase.

Of note: Tumor lesions previously irradiated or subjected to other locoregional therapy will only be deemed measurable if progression as per RECIST 1.1 at the treated site after

completion of therapy is clearly documented. A target lesion biopsied during the screening period will NOT be considered as a measurable lesion.

Active Treatment Phase Tumor Assessments will include:

- Imaging assessments of chest, abdomen and pelvis (CAP) by CT or MRI mandatory.
- CT/MRI scan of any other sites of disease (including brain), if lesions identified at screening assessment.
- Clinical assessment of superficial lesions, if lesions identified at screening.
- Bone scan, mandatory only if it is the preferred technique to follow bone lesions identified at screening.

CT/MRI and bone scans (as applicable and if bone scan is the preferred technique to follow them on treatment) must be repeated on treatment as per Table 2 (every 8 weeks for the first 48 weeks from the date of randomization and then every 12 weeks thereafter for CT/MRI and every 24 weeks for bone scan from the date of randomization) until radiographically and/or clinically (eg for photographed or palpable lesions) documented PD as per RECIST v1.1, study treatment discontinuation (for participants continuing treatment beyond RECIST-defined disease progression, see Section 8.2.1.1), or discontinuation of participant from overall study participation (ie, death, participant's request, lost to follow up), whichever occurs first.

CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response.

Brain scan or scans of any other anatomical site will be repeated on the active treatment phase only if lesion/s present at screening or new lesions are suspected.

Clinical assessment of superficial disease should be carried out preferably on the same date.

If no bone lesions were identified at screening, bone scans will only be repeated during the active treatment phase when clinically indicated (ie, participant describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) or at the time of confirmation of CR. Any suspicious abnormality identified by bone scan on treatment, must also be confirmed by X-ray, CT scan with bone windows or MRI.

Further imaging assessments may be performed at any time if clinically indicated (eg, suspected PD, symptomatic deterioration, etc).

Participants who have already demonstrated objective disease progression as per RECIST v1.1 are expected to discontinue study therapy and begin the follow up phase of the trial. See Section 8.2.1.1 for treatment continuation beyond progression.

For participants who do NOT have documented objective disease progression at time of study treatment discontinuation, tumor assessment will continue to be performed as per Table 2 (every 8 weeks for the first 48 weeks from date of randomization and then every 12 weeks thereafter for CT/MRI and every 24 weeks from date of randomization for bone scan) until radiographically and/or clinically (eg, for photographed or palpable lesions) confirmed objective disease progression, or discontinuation of participant from overall study participation (e.g., death, participant's request, lost to follow up).

For participants having effusions or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumor assessment CRFs. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion CRF.

BICR will review all radiological images as well as other information as per section 8.2.1.2. All radiographic images as well as other information will be collected and objectively verified by an independent third-party core imaging laboratory as described in the Study Imaging Manual.

Objective tumor response will be measured using Response Evaluation Criteria in Solid Tumor (RECIST v1.1) (also refer to Appendix 13).

All participants' files and radiologic images and pathology samples must be available for source verification and for potential peer review.

8.2.1.1. Treatment Beyond Progression in Both Arms

Participants should be discontinued from study intervention when investigator assessed PD. However, participants with disease progression by RECIST v1.1 who are continuing to derive clinical benefit from the study intervention (ie, positive benefit/risk assessment as assessed by investigator) according to the investigator's clinical judgment, may be eligible to continue study intervention (crossover between treatment arms is not permitted) after discussion between the investigator and the sponsor medical monitor. The investigator's judgment should be based on the overall benefit/risk assessment for study intervention continuation considering the participant's clinical condition, including performance status, clinical symptoms, AEs and laboratory data.

The participant must consent to continue treatment beyond progression.

Participants who continue treatment after progression should discontinue study intervention upon evidence of further progression by imaging as per RECIST v1.1 as outlined in Appendix 13, from time of initial PD, or worsening of participant's clinical condition suggesting a negative benefit/risk assessment for study intervention continuation, unless otherwise agreed between the investigator and the sponsor medical monitor.

In participants who continue treatment beyond progression, the oncologic assessments (as well as the other safety assessments as per Active Treatment Phase) should continue to be

performed as per Table 2 and recorded in the CRF until the study intervention is permanently discontinued.

8.2.1.2. Independent Review of Disease Assessments

A blinded independent third-party central imaging laboratory will perform a review of radiographic images as well as all the other information reported below collected on study to determine the protocol defined endpoints of disease response and progression.

It is important to the integrity of the study that all imaging studies, clinical assessment of superficial lesions and clinical information (as applicable) are provided to BICR on an ongoing basis (as soon as they are available) until confirmation of objective disease progression by BICR as per RECIST v1.1, regardless of the initiation of a new anticancer therapy.

The following materials need to be forwarded for BICR of images:

- All imaging studies performed on study
- clinical assessment of superficial lesions
- Clinical information, as applicable.

8.2.1.2.1. Expedited Blinded Independent Central Review for Disease Progression

To mitigate the potential for bias in determining disease progression, expedited BICR review will be performed for investigator assessed disease progression. Upon investigator assessed disease progression, the radiographic image as well as all the other information as reported in the Section 8.2.1.2 will be submitted to the BICR for expedited review. See the Study Imaging Manual for process details.

8.2.1.3. Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study.

Tumor assessment images will be reviewed by a central review facility. The purpose of this review is to evaluate images for disease assessment. Central image review is not a complete medical review of the participant, and no incidental findings will be shared with the PI, site staff, or the participant. All safety reviews will be the sole responsibility of site staff.

8.2.1.4. Alternative Facilities for Tumor Assessment

Tumor assessment may be performed at an alternative facility as long the equipment is adequate (eg, qualification/calibration/maintenance) and the images can be uploaded to the investigative site for overall tumor response assessments and for submission to the BICR (see Section 8.2 and Section 8.2.1.2), if approved upon written confirmation from the sponsor.

8.2.2. Survival Follow-up Analysis

The study Survival Follow-up period will conclude at the time of the final OS analysis (See Section 9.3.3.1).

8.3. Safety Assessments

Planned time points for all safety assessments are provided in Table 2. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

At screening, a complete physical will include assessments of all the major body systems. The complete physical examination should include the examination of general appearance (head, eyes, ears, nose, mouth, throat, skin, heart, lung, lymph nodes, gastrointestinal, genitourinary, neurologic, and muscle-skeletal). Sites of disease identified by physical examination will be recorded on the tumor assessment pages and recorded as Target or Non-target lesion. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height and weight will be collected as per Table 2. For measuring weight, a scale with appropriate range and resolution must be used and 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.

PEs may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. On dosing days physical examinations must be performed prior to study intervention administration.

Symptom-directed physical examinations will be performed at subsequent visits as per Table 2. Additional physical examinations may be performed if clinically indicated.

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

8.3.2. Vital Signs

Vital signs will be measured per institutional standards and will include systolic and diastolic blood pressure, and pulse rate.

All vital sign measurements as per Table 2 should be performed prior to study intervention administration.

Vital signs will be assessed while the participant is in a sitting position or semi-recumbent position (recommended). It is recommended that the same position be used consistently throughout the duration unless circumstances, e.g., hospitalization, dictate otherwise.

Vital signs should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Abnormal readings should be repeated and confirmed.

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

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in Table 3 using the study ECG machine supplied by the Sponsor that automatically calculates the mean heart rate and measures QTc interval and also collects QT interval, PR interval, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement.

All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position. Triplicate ECGs are defined as three consecutive ECGs performed approximately 2 minutes apart but within 10 minutes for all 3 measurements as per Table 3 to determine the QTc interval. Blood sample for electrolytes (sodium, potassium, magnesium, total calcium) must be collected at Day 1 (-2 days) pre-dose of the required cycles (see Table 3 for details).

The ECGs tracings for all participants (including the participants belonging to the QTc Sub-study) will be read and interpreted by qualified personnel at investigational site to determine eligibility and for safety monitoring.

ECG assessment will be performed as follows:

- Approximately the first 80 participants in Arm A at selected sites will have their QTc monitored to evaluate the effect of ARV-471 on QT interval via triplicate ECGs time-matched with PK draws (QTc sub-study). ECGs will be obtained as specified in Table 3. **All ECGs (with the exception of the ECG performed at screening) should be obtained after a fast of at least 1 hour**. ECGs should be performed immediately before PK blood draws at respective time points. All triplicate ECGs will be electronically transmitted to the central ECG vendor for storage and analysis. The anonymized semi-manual interval measurements of the ECG performed at each time point (with the exception of the ECG performed at screening) and obtained from the central ECG laboratory will be used for primary statistical analysis of ECG data. The Investigator should review and sign the ECG tracings and final ECG report from the vendor (and file them with the participant's source documents).

- All the remaining participants in Arm A and those in Arm B will have triplicate ECGs performed as per Table 3. No central reading is required, but ECGs will be electronically transmitted the to the central ECG vendor for storage.
  ECGs should be performed immediately before PK blood draws at respective time points (Arm A).

When an ECG is to be performed at the same time point as a blood collection (eg, safety laboratory assessments, PK samples), the ECG is to be performed first prior to the nominal time of the blood collection.

At any time, additional triplicate ECGs as well as electrolytes laboratory assessments (ie, sodium, potassium, magnesium, total calcium) may be performed as clinically indicated.

The ECG must be reviewed by qualified personnel at the site as soon as any abnormality is observed, including verifying that the machine reading is accurate, and that the Fridericia correction formula is applied. In some cases, it may be appropriate to repeat abnormal ECGs (ie at least two times approximately 2 minutes apart) 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 readings confirm a QTc of ≥ 501 msec or >60 msec change from baseline, immediate search for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs that may potentially prolong the QTc interval) should be performed. Repeat ECG should be performed when one of the following conditions apply:

- When a post dose QTc interval remains > 60 msec from the baseline OR is ≥501 msec, repeat ECGs should be performed immediately as per the investigator's best medical judgement until the QTc interval is ≤ 60 msec from the baseline or QTc interval falls ≤ 480 msec
- QTc intervals get progressively longer.

A cardiologist should be consulted if QTc intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator). If QTc interval reverts to less than 501 msec or ≤ 60 msec change from baseline, and in the judgment of investigator(s) in consultation with the sponsor medical monitor the cause is determined to be other than study drug, treatment may be continued with regular ECG monitoring under hospital supervision.

Prior to concluding that an episode of prolongation of the QTc interval is due to study intervention, thorough consideration should be given to potential precipitating factors (eg, change in participant clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist should be performed.

If study intervention causality cannot be ruled out, study intervention dose modifications and/or interruption or permanent discontinuation, as applicable, should be performed

according to instructions provided in Table 7 for ARV-471 in Arm A or on the Faslodex EU SmPC for fulvestrant in Arm B, as applicable.

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

8.3.3.1. Alternative Facilities for Electrocardiograms

The participant may visit an alternative facility to have the ECGs performed (see Section 8.1.5) only when an unscheduled ECG is done as clinically indicated (ECG scheduled as per Table 3 cannot be performed in alternative facilities) . Qualified study site personnel must order, receive, and review results. ECGs can also be performed at home through home health vendors or through remote device collection, upon written confirmation from the sponsor.

Tests results are to be provided to the site staff as soon as possible. Participants should be instructed to bring original reports in at the next visit. ECG reports should be filed in the participant's source documents/medical records. Relevant data from the ECG report should be recorded on the CRF.

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

8.3.4. Clinical Safety Laboratory Assessments

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

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

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

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

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

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

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Protocol-specified safety laboratory evaluations as per Table 2 may be conducted at a local laboratory, if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital.

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. Participants should be instructed to bring original reports in at the next site visit. 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.

8.3.5. Pregnancy Testing

A serum pregnancy test is required at screening (Table 2). Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. 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. Pregnancy tests will be performed in WOCBP at the times listed in Table 2.

Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at baseline visit prior to starting the study intervention. Pregnancy tests will be done until 28 days after the last dose.

Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

8.3.5.1. At-Home Pregnancy Testing

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 and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

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

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 9. Device deficiencies are covered in Section 8.4.9.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally

authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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

During the active collection period as described in Section 8.4.1, each participant or 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.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 28 calendar days after the last administration of the study intervention.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form/ PSSA.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form/ PSSA immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

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.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

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.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by, skin contact, ingestion or injection.

    - A male family member or healthcare provider who has been exposed to the study intervention by, skin contact, ingestion, or injection then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form/PSSA and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 28 days after the last dose of ARV-471 and for at least 9 months after the last dose of fulvestrant.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form/PSSA 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/PSSA 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. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures

for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

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/PSSA. 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/PSSA is maintained in the investigator site file.

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

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form/PSSA, 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/PSSA must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Cardiovascular events will be reported as AE/SAE as per Section 8.4.6 and Appendix 3. Cardiovascular events are to be managed per the dose modifications outlined in Section 6.6. AEs and SAEs that result in death are to be reported per guidelines as outlined in Section 8.4.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

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

AESIs for fulvestrant and mitigation strategies are summarized in Section 2.3.1.

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

8.4.8.1. 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**.

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 9.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Section 8.4.1 through 8.4.4 and Appendix 3 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 9.

8.4.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.4.9.3. Prompt Reporting of Device Deficiencies

When a device deficiency occurs:

1. The investigator notifies the sponsor by contact method, eg, telephone, email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint form.

3. If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see 8.4.1.1 All relevant details related to the role of the device in the event must be included in the CT SAE Report Form /or via PSSA as outlined in Section 8.4.1.1and 8.4.1.2. The sponsor will be the contact for the receipt of device deficiency information.

8.4.9.4. Regulatory Reporting Requirements

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention (ie, incorrect randomized assignment, or incorrect study intervention being used in this study);
- The administration of an incorrect dosage defined as underdose (see Section 6.5) or overdose (See Section 6.8);
- Device deficiency.

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF which is a specific version of the AE page and, if applicable, any associated serious and nonserious, AE(s), are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form/PSSA **only when associated with an SAE.**

8.5. Pharmacokinetics

Pharmacokinetics will be assessed in Arm A only. A single 3 mL whole blood sample at each time point will be collected for determining concentrations of ARV-471 and ARV-473 as specified in Table 3. The 3 mL blood samples to provide approximately 1.5 mL plasma will be collected into appropriately labeled tube containing K2 EDTA for ARV-471 and ARV-473. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the sampling time window specified in Table 3 will not be considered protocol deviations as long as they have a documented actual time and date of collection and relevant time and date of dosing.

On visit days, participants must be instructed to not take their ARV-471 dosing and to wait to take their daily dose of ARV-471 until the pre-dose assessments listed in Table 2 and Table 3 have been completed. On these days, ARV-471 dose should be taken under the supervision of the study personnel.

PK draws will be done immediately after triplicate ECGs have been performed at all time points so that the PK samples are collected at the nominal time.

The actual time of the sample collection and the most recent dosing time before and after each collection will be recorded on the eCRF. The date of missing/reduced dose should also be recorded in the eCRF.

If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor. In addition to samples collected at the scheduled times, every effort should be made to collect an additional blood sample from participants experiencing unexpected and/or serious AEs and to document the date and time of sample collection and of last dosing prior to PK collection on the CRF.

Samples collected for concentration analyses of ARV-471 and its epimer, ARV-473, may also be used to evaluate safety or efficacy aspects related to concerns arising during or after

the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of ARV-471 and its epimer, ARV-473, will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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 (ie, 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. Refer to Laboratory Manual for detailed collection, processing, and shipping procedures.

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

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic (analyses) are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A single 4-mL whole blood sample optimized for DNA isolation Prep D1; K2 EDTA will be collected according to Table 2, as local regulations and IRBs/ECs allow.

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

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in Laboratory Manual.
NOTE: Retained Research Samples for genetics are not applicable for participants in China.

8.7. Biomarkers

Tumor tissues and/or blood samples will be used to evaluate biomarkers (genes and proteins) involved in the biology of the participant's disease, and mechanisms of sensitivity or resistance to ARV-471, to conduct genomic, and/or molecular profiling analyses. The biomarkers involved in cellular proliferation, oncologic driver, and immunologic regulations, for example, but not limited to, Ki67 for protein marker, ESR1 and PIK3CA gene mutations, will be investigated. In addition, the quantitative changes (on treatment from baseline) of cell free tumor DNA concentration in the participant's blood will be analyzed to estimate its potential as treatment responses. Refer to Table 2 for sample collection time points and Laboratory Manual for sample processing and shipping.

Unless prohibited by local regulations or IRBs/ECs, the following samples for biomarker research are required and will be collected from all participants in this study as specified in Table 2:

- Tumor Biopsy- See Section 8.7.1
- Blood samples See Section 8.7.2

Optional samples for biomarker research that should be collected from participants in the study as appropriate are the following:

- Tumor tissue sample collection at the EOT visit.

Additional information on tissue collection procedures, sample preparations including processing, storage, and shipment to the sponsor designated laboratories for biomarkers analysis will be provided in the Laboratory Manual.
Note: for participants in China, sample collection for biomarkers and biomarker testing will not be performed unless approved by HGRAC.

8.7.1. Tumor Biopsies

Tumor biopsy collected at the time of presentation with locoregional recurrent, or metastatic disease is mandatory for study participation. If no tissue taken at the time of presentation with locoregional recurrent/metastatic disease is available a de novo biopsy is needed at screening.

Exception: for participants with bone lesions only and for participants in whom the collection of a biopsy is clinically contraindicated an archival tumor tissue (ie tumor sample from initial diagnosis) is acceptable.

Only core needle or excisional biopsies, or resection specimen are suitable. Cytologic preparations, such as fine needle aspirate biopsies, are not acceptable.
Bone biopsies are not acceptable since the decalcification process renders the sample unusable for biomarker analysis.

For all participants submission of FFPE tumor samples (blocks or 15 unstained slides [10 minimum] of 5 micron thickness on positively charged slides) will be required. Collected samples will be sent to the sponsor designated laboratories for assessment of biomarkers.

An optional de novo tumor biopsy may be collected at the EOT visit only for participants who discontinue treatment due to disease progression and when, in the investigator's judgment, such biopsy is feasible and can be safely performed. The EOT tumor tissue will be used to determine possible mechanisms of resistance. Tissue samples from all participants will be used for additional biomarker analyses.

8.7.2. Blood Samples

The peripheral blood and derivatives may be used to characterize potential correlations of tumor molecular profile and ctDNA level with response to study treatment and to understand potential mechanisms of acquired resistance to study treatment. Assessment of the relationship between ctDNA burden and outcome is a secondary objective of this study. Additional analyses may be warranted based on emerging data.

Two 10 mL whole blood samples (one 10 mL sample for China) optimized for plasma preparation for ctDNA analysis will be collected pre-dose at each time point as per Table 2. DNA samples will be analyzed for the purpose of tumor molecular profile and the assessment of quantitative changes in plasma ctDNA following treatment with ARV-471.
C1D1 samples may also be used for the development of companion diagnostics, if needed.
For China the ctDNA sample collected during the pre-screening period may be also used for tumor molecular profile/ctDNA level and ctDNA burden if the participants are randomized in the trial.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

PRO assessments will be administered to evaluate the impact on quality of life, functioning, symptoms, and general health status using the Dimension Health State EuroQoL Score (EQ-5D-5L) and EORTC QoL questionnaires (QLQ-C30 and QLQ-BR23 (female and male questionnaire versions) and BPI-SF. The mBPI-SF (worst pain severity [item 3] and pain interference [item 9a]), and pain medication usage (Arm A and Arm B) and injection site pain (Arm B only) will also be captured using an evening daily diary (Table 2). Preference for route of administration (Arm A and Arm B) will be evaluated using a patient preference questionnaire.

Self-assessment questionnaires (EQ-5D-5L, QLQ-C30, QLQ-BR23, BPI-SF and patient preference questionnaire) should be completed by the participants before any other study activities or medical procedures as per Table 2.

Refer to Appendix 14 for further information on the PRO assessments administered.

9. STATISTICAL CONSIDERATIONS

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

The study will perform the statistical hypotheses tests for primary endpoint (PFS) and the key secondary endpoint (OS) in two participant populations: 1) all randomized participants, and 2) participants with ESR1 mutation.

9.1. Statistical Hypotheses

PFS assessed by BICR as per RECIST v1.1 will be the primary endpoint for the study.

The study is designed to test the null hypothesis vs. the alternative hypothesis for PFS noted below in each of the two participant populations: 1) all randomized participants, and 2) participants with ESR1 mutation. The following statistical hypotheses will be tested to address the primary objective:

$H_{0\ \text{all participants}}$: $HR_{PFS} \geq 1$ vs $H_{1\ \text{all participants}}$: $HR_{PFS} < 1$

$H_{0\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{PFS} \geq 1$ vs $H_{1\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{PFS} < 1$

where HR_{PFS} is the hazard ratio (ARV-471 vs fulvestrant) of PFS.

As the key secondary endpoint, the study is also designed to test the null hypothesis vs the alternative for OS noted below in each of the two participant populations: 1) all randomized participants, and 2) participants with ESR1 mutation.
The following statistical hypotheses will be tested to address this key secondary objective for OS:

$H_{0\ \text{all participants}}$: $HR_{OS} \geq 1$ vs $H_{1\ \text{all participants}}$: $HR_{OS} < 1$

$H_{0\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{OS} \geq 1$ vs $H_{1\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{OS} < 1$

where HR_{OS} is the hazard ratio (ARV-471 vs fulvestrant) of OS.

Evaluation of treatment effect in participants without ESR1 mutation:

The study is not designed for a formal hypothesis testing in participants without ESR1 mutation. However, to address emerging evidence of differential efficacy of SERDs in ESR1 mutation positive vs ESR1 mutation negative participants, a minimum efficacy effect is pre-specified following Rothmann criteria for the subgroup of participants ESR1 mutation negative (McShane et al, 2023). Specifically, the minimum effect size of PFS is set to be HR ≤ 0.789, which is the critical HR boundary of the hypothesis testing for all participants population with 3/4 α level and 310 PFS events.

9.1.1. Estimands

9.1.1.1. Primary Estimand/Coprimary Estimands

The primary estimand of this study is based on a hypothetical strategy, which estimates the treatment effect if participants maintain their randomized treatment and adhere to the protocol. The estimand is defined according to the primary objective and is in alignment with the primary endpoint.

Treatment: ARV-471 vs fulvestrant

Population: Participants with ER(+)/HER2(-) advanced breast cancer who have progressed after prior endocrine-based treatment(s) for their advanced disease, in 1) all randomized participants, and 2) randomized participants with ESR1 mutation.

Variable: BICR-assessed PFS defined as the time after randomization to the first documentation of objective PD per RECIST v1.1, or death due to any cause, whichever occurs first.

Intercurrent events: PFS data will be censored on the date of the last adequate tumor assessment for participants with the following intercurrent events

- Discontinue the study treatment due to withdrawal of consent prior to an event
- Start a new anti-cancer therapy prior to an event
- Have an event after an unacceptably long interval (2 or more missing, incomplete or non-evaluable assessments)
- Lost to follow-up

Population-level summary: A stratified log-rank test will be used to compare PFS between the two treatment arms. HR for PFS with the corresponding 2-sided 95% CI will be calculated based on Cox's proportional hazard model. PFS time associated with each treatment arm will be summarized using the Kaplan-Meier method and median PFS time with the corresponding 2-sided 95% CI will be reported.

9.1.1.2. Secondary Estimands

The key secondary estimand of this study is defined according to the secondary objective for OS and is in alignment with the secondary endpoint OS. This secondary estimand is based on a treatment policy strategy, which estimates the treatment difference regardless of whether an intercurrent event occurs.

Treatment: ARV-471 vs fulvestrant

Population: Participants with ER(+)/HER2(-) advanced breast cancer who have progressed after prior endocrine-based treatment(s) for their advanced disease in 1) all randomized participants, and 2) randomized participants with ESR1 mutation.

Variable: OS defined as the time from the date of randomization until the date of death due to any cause. Survival status is expected to be collected irrespective of study treatment discontinuation or participant's request to discontinue study procedures. All participants who

have not withdrawn consent for further participation in the study should be followed for survival until the end of the study.

Intercurrent events: All data will be used regardless of the occurrence of intercurrent events (discontinuation of study treatment, use of subsequent treatments, discontinuation of study, etc.)

Population-level summary: A stratified log-rank test will be used to compare OS between the two treatment arms. HR for OS with the corresponding 2-sided 95% CI will be calculated based on Cox's proportional hazard model. OS time associated with each treatment arm will be summarized using the Kaplan-Meier method and median OS time with the corresponding 2-sided 95% CI will be reported.

9.1.2. Multiplicity Adjustment

The study will perform the following statistical hypotheses tests.

Primary endpoint family:

$H_{0\ \text{all participants}}$: $HR_{PFS} \geq 1$ vs $H_{1\ \text{all participants}}$: $HR_{PFS} < 1$

$H_{0\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{PFS} \geq 1$ vs $H_{1\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{PFS} < 1$

And secondary endpoint family:

$H_{0\ \text{all participants}}$: $HR_{OS} \geq 1$ vs $H_{1\ \text{all participants}}$: $HR_{OS} < 1$

$H_{0\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{OS} \geq 1$ vs $H_{1\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{OS} < 1$

The four null hypotheses are denoted by H_1 through H_4 and are grouped into two families (primary efficacy endpoint PFS and key secondary efficacy endpoint OS). The null hypotheses H_1 and H_3 correspond to the comparisons in ESR1 mutant population, while H_2 and H_4 correspond to the comparisons in ITT population.

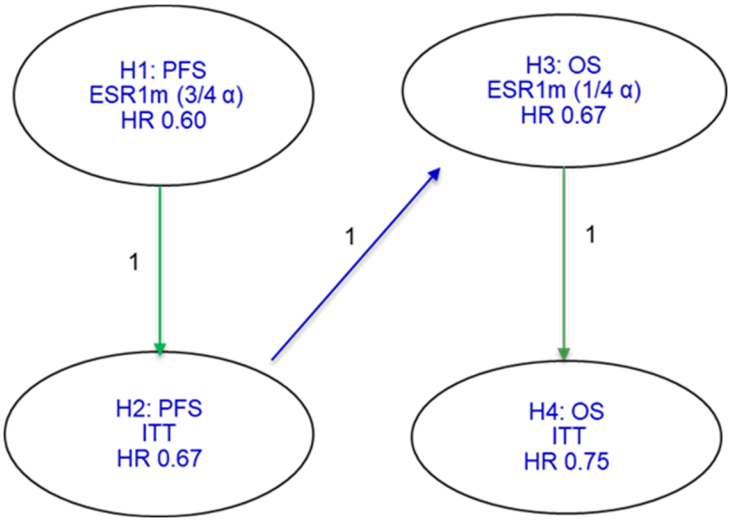
	ESR1 mut	ITT
PFS family	H_1	H_2
OS family	H_3	H_4

To control the family-wise type I error rate within 0.025 (1-sided) at the whole study level, a graphical multiple testing strategy will be used. Specifically, 3/4 α (0.01875) is allocated for PFS endpoint family to test superiority of PFS by BICR and 1/4 α (0.00625) is allocated for OS endpoint family to test superiority of OS (see Figure 1).

Within each endpoint family, a gate keeping procedure will be applied in which the ESR1 mutation positive population will be tested first. If positive, the ITT population will then be

tested. The significance level for PFS family is 3/4 α (0.01875). The significance level for OS family depends on the results from the PFS family. If the PFS tests are positive in both testing populations, 3/4 α used for PFS testing will be reallocated to OS endpoint family and OS can be tested with full α (0.025). Otherwise, only the original allocated 1/4 α (0.00625) will be used for OS test.

Figure 1. Statistical hypothesis testing strategy



Note: value 1 in the figure between the hypotheses (circles) represent the full amount of alpha to be passed from one hypothesis test to the next when the hypothesis test is positive.

No interim analysis is planned for the primary endpoint PFS.

Two interim analyses for efficacy are planned for the key secondary endpoint of OS in each co-primary population: ESR1 mutant subgroup and all participants population. The Lan-DeMets/O'Brien-Fleming boundary will be used to control alpha spending for the second OS interim analyses in both populations. See Section 9.4 Interim Analysis.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention.
Full Analysis Set	All enrolled participants who were randomized. Participants are analyzed according to the treatment they have been randomized to receive.

Participant Analysis Set	Description
Safety Analysis Set (SAS)	All randomized participants who receive at least 1 dose of study intervention.
PK Concentration Set	All participants who are in the Safety Analysis Set and have at least 1 concentration of either ARV-471 or ARV-473.
QTc Analysis Set	A subset of SAS participants in Arm A, who are randomized at selected sites and have ECG measurements to evaluate the effect of ARV-471 on QT interval via triplicate ECGs, must have baseline ECG measurement (Cycle 1 Day 1 pre-dose) and at least one ECG measurement on Day 1 of Cycle 2 or Cycle 3.
Biomarker Analysis Set(s)	Biomarker analysis population is defined as all randomized participants with at least 1 of the Biomarkers evaluated at pre and/or post dose.
PRO Analysis Set	The PRO analysis set will include all participants in the full analysis set who completed a baseline (PRO assessment prior to or on first dose of study treatment) and at least one post-baseline PRO assessment.

9.3. Statistical Analyses

The SAP will be developed and finalized before any formal statistical 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

All efficacy analyses will be performed using the FAS, and all safety analyses will be performed using the SAS. Statistical analyses will be performed in each of the two populations: 1) all randomized participants, and 2) participants with ESR1 mutation.

In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

All primary and secondary endpoints based on radiological assessments of tumor burden (ie, PFS, OR, DOR, CBR) will be based on BICR assessments as per RECIST v1.1.

Tumor assessments based on programmatically derived version of local radiologist's /investigator's assessment (target lesion measurements, non-target lesion status, and new lesion status recorded on the CRF) will be used as sensitivity analyses to support the primary analyses.

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

The primary endpoint is - PFS assessed by BICR which is defined as the time from the date of randomization to the date of the first documentation of objective PD per RECIST v1.1, or death due to any cause, whichever occurs first, in each of the two populations: 1) all

randomized participants, and 2) participants with ESR1 mutation. The final PFS analyses will be performed when the required number of events are reached in both testing populations.

PFS will be calculated in months as:

PFS (months) = (date of event or censoring– randomization date +1) / 30.4375

PFS will be censored on the date of the last adequate disease assessment for participants who do not have an event (PD per RECIST v1.1 or death due to any cause), before the new anticancer therapy for participants who start a new anticancer therapy prior to an event, or before the gap for participants with an event after a gap of 2 or more missing disease assessments. Participants who do not have an adequate post-baseline disease assessment will be censored on the date of randomization unless death occurs on or before the time of the second planned disease assessment (ie, ≤18 weeks after the date of randomization) in which case the death will be considered an event.

The treatment effect HR will be estimated using a Cox's proportional hazard model stratified by randomization strata to calculate the hazard ratio for PFS, along with the 95% corresponding 2-sided CI.

PFS time will be estimated using the Kaplan-Meier method and displayed graphically by treatment arm. The median PFS and associated 95% CIs will be presented by treatment arm.

Per regulatory request, a supplemental analysis will be performed based on a treatment policy strategy, which estimates the treatment difference regardless of whether an intercurrent event occurs. In this supplemental analysis, any PD or deaths captured in the study will be counted as PFS events regardless of protocol violations, discontinuation of study treatments, or receiving new anti-cancer therapies. The details of the analysis will be specified in SAP.

Sensitivity analyses for PFS (including PFS assessed by investigators) will be specified in the SAP.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

9.3.3.1. Key Secondary Efficacy Endpoint

OS is the key secondary endpoint. The study is also designed to perform the hypothesis testing to demonstrate that ARV-471 is superior to fulvestrant in prolonging OS in participants with ER(+)/HER2(-) advanced breast cancer whose disease has progressed on prior endocrine treatment(s) in each of the two populations: 1) all randomized participants, and 2) participants with ESR1 mutation. The final OS analyses will be performed when the required number of events are reached in both testing populations.

OS is defined as the time from date of randomization to date of death due to any cause. OS will be calculated in months as:

OS (months) = [date of death or censoring – date of randomization +1] / 30.4375

For participants without documented death, OS time will be censored on the date last known to be alive.

The treatment effect HR will be estimated using a Cox's proportional hazard model stratified by randomization strata to calculate the hazard ratio for OS, along with the 95% corresponding 2-sided CI and RCI.

OS time will be estimated using the Kaplan-Meier method and displayed graphically by treatment arm. The median OS and associated 95% CIs will be presented by treatment arm.

Sensitivity analyses for OS will be specified in the SAP.

9.3.3.2. Other Secondary Endpoints

9.3.3.2.1. ORR/DOR/CBR

ORR is defined as the proportion of participants in the FAS reaching a confirmed CR or PR by BICR assessment as per RECIST v1.1 criteria. Point estimates of ORR will be calculated along with the 2-sided exact 95% CIs using the Wilson Score method. The odds ratio and the corresponding 2-sided 95% confidence interval will be calculated to contrast the treatment effects on response rates. A Pearson test (un-stratified) and CMH test stratified by randomization stratification factors will be used to compare ORR between the two arms.

ORR will be summarized in each of the two populations: 1) all randomized participants, and 2) participants with ESR1 mutation.

DOR will be summarized using the Kaplan-Meier methods and displayed graphically where appropriate. DOR will be calculated for the subgroup of participants with objective tumor response (CR/PR) by BICR assessment. The median event time and 2-sided 95% confidence interval for the median will be provided. DOR analyses will be performed in each of the two populations: 1) all randomized participants, and 2) participants with ESR1 mutation.

CBR: CBR is defined as confirmed CR or PR at any time, or SD/Non-CR/Non-PD (for participants with non-measurable disease) ≥24 weeks according to the RECIST version 1.1 recorded in the time period between randomization and disease progression by BICR assessment, or death of any cause, whichever occurs first. The number and proportion of participants achieving clinical benefit response (confirmed CR or PR at any time, or SD/Non-CR/Non-PD ≥24 weeks) will be summarized in the FAS population along with the corresponding 2-sided 95% confidence interval calculated using the Wilson score method. The odds ratio and the corresponding 2-sided 95% confidence interval will be calculated to contrast the treatment effects on CBR rates. A Pearson test (unstratified) and CMH test stratified by randomization stratification factors will be used to compare CBR rate between the treatment arms. CBR analyses will be performed in each of the two populations: 1) all randomized participants, and 2) participants with ESR1 mutation.

9.3.3.2.2. Pharmacokinetic Analysis

Plasma concentration data of ARV-471 and ARV-473 will be listed, summarized, and plotted for all participants in the PK concentration set as defined in Section 9.2. For summary

statistics and mean/median plots by collection time/day, the nominal PK sample collection time/day will be used; for individual participant listing by time/day, the actual PK collection time/day will be used. PK sampling deviations from the protocol-specified collection time/day will be listed.

PK data from participants in the Arm A QTc sub-study will be analyzed separately according to the method described above.

Population pharmacokinetic analysis of samples collected in this study will be performed in accordance with the FDA guidance on Population Pharmacokinetics (FDA, 2022). The PK concentration data set from this study may be pooled with datasets from other ARV-471 clinical studies. In addition, population PK/PD modeling will be attempted to investigate any causal relationship between ARV-471 and/or ARV-473 exposure and biomarker, safety, efficacy, and/or laboratory data. These modeling analyses will be reported separately from the final Clinical Study Report.

9.3.3.2.3. PRO data analyses

The following patient reported outcome measurements will be collected in this study: EORTC QLQ-C30, EORTC QLQ-BR23 (female and male questionnaire versions), EQ-5D-5L, and BPI-SF. The mBPI-SF (worst pain severity [item 3] and pain interference [item 9a]), pain medication usage and patient preference questionnaire (Arm A and Arm B) and injection site pain (Arm B only) will be captured as well. The analysis of the patient preference questionnaire and evening daily diary will be described in a separate SAP.

For each of the four measurements (EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L, and BPI-SF), mean scores at each assessment time point and change from baseline scores will be compared between the treatment arms at various time points using a MMRM approach adjusting for specified covariates. In addition, analyses will be performed to determine if the change from baseline scores achieves the appropriate clinically meaningful threshold for the scale being examined. Participants who completed a baseline assessment and at least one post baseline assessment will be considered evaluable for the change from baseline analysis. In addition to the above analyses, an examination of the TTD also will be carried out using survival analysis methods. Deterioration will be defined based on clinically meaningful threshold. For the EORTC QLQ-BR23, female and male questionnaires will be analyzed separately.

9.3.3.2.4. ctDNA analysis

Analysis summaries of baseline levels, changes from baseline (where appropriate), and their association with efficacy outcome will be reported.

9.3.3.2.5. Safety analysis

All safety analyses will be performed on the SAS. Summaries of AEs and other safety parameters will be provided as appropriate.

9.3.3.2.5.1. Adverse Events

AEs will be coded using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v5.0 whenever possible. 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, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs on the entire study period.

9.3.3.2.5.2. 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.

9.3.3.2.5.3. Summary and Categorical Analysis of ECG

All participants in the safety analysis set with baseline and on-treatment ECG data will be included in the ECG summary and analysis. The triplicate data will be averaged, and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

Individual change in QTcF (and QTcS, as appropriate) will be calculated for each nominal time point. These individual changes will be summarized using descriptive statistics.

Categorical analysis of the ECG data will be conducted and summarized as follows:

1. The number and percentage of participants with maximum increase from baseline in the QTc (<30, 30-60, and >60 ms).

2. The number of and percentage participants with maximum post-dose QTc (<450, 450-<480, 480- <501, and ≥501 ms).

3. PR changes from baseline ≥50% if absolute baseline value was <200 ms, and ≥25% if absolute baseline value was >200 ms.

4. QRS changes from baseline ≥50% if absolute baseline value was <100 ms, and ≥25% if absolute baseline value was >100 ms.

Central tendency of the effect of ARV-471 on the QT/QTc interval will be summarized by the mean (90% CI) change from baseline at each timepoint.

ECG measurements scheduled as per protocol (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

The analyses described above will be repeated separately for the QTc Analysis Set using centrally-read ECG data.

9.3.3.2.5.3.1. Electrocardiogram Analyses for QTc Analysis Set

Centrally-read QT measurements corrected by heart rate (QTc) will be used for the data analysis and interpretation and Fridericia's (QTcF) method will be used for the primary analysis. In addition, a study specific correction method (QTcS) may be used for the exploratory analysis.

At each ECG measurement time point, a total of 60 evaluable participants is estimated to provide an upper limit of 90% confidence interval of 8 msec for a mean increase of 5 msec, or 10 msec for a mean increase of 7 msec in from baseline QTcF, based on an estimated standard deviation of 14 msec for the change in QTcF from Study ARV-471-mBC-101. Approximately 80 participants will be enrolled to ensure at least 60 participants are evaluable for the QTc analysis.

The changes in QTcF (and QTcS, as appropriate) on Day 1 of Cycle 2 and Cycle 3 from baseline will be summarized using descriptive statistics and categorical analysis by each time point.

9.3.3.2.5.3.2. Pharmacokinetic/Pharmacodynamic Analysis of QTc

Concentration-QTc analysis will be conducted using PK- matched ECG data from the Safety Analysis Set. Linear, log-linear, and/or saturable models will be examined for the concentration-QTc relationship. Exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model. Diagnostic evaluation will be included to explore the adequacy of the model. Refer to SAP for details of the analysis. The modeling analyses may be reported separately from the clinical study report.

9.3.4. Other Analysis

Retained Research Samples may be collected as per Table 2 and retained for future analyses. The results of such analyses are not planned to be included in the CSR.

9.3.5. Exploratory Analysis

9.3.5.1. Biomarker Analyses

Biomarker data, including but not limited to DNA, RNA, and protein from analyses of tumor tissues and/or blood samples will be analyzed. Analysis summaries of baseline levels,

changes from baseline (where appropriate), and mutation status will be reported. For continuous variables, summary statistics may include, but not limited to the mean, standard deviation, median, 25th and 75th quartile, minimum and maximum levels of biomarker measures; for categorical variables, summary may include number and percentage, odds ratio as appropriate. Exploratory graphical methods and statistical methods such as, but not limited to linear regression, t-test, and ANOVA may be used to investigate any possible relationship of biomarker levels and status and/or changes from baseline with ARV-471 anti-tumor efficacy and other clinical outcomes. Results of such analyses may not be included in the CSR.

9.4. Interim Analysis

No interim analysis is planned for the primary endpoint PFS.

Two interim analyses for efficacy are planned for the key secondary endpoint of OS.

The first OS interim analysis (IA1) will be performed at the time of the final PFS analysis for both co-primary populations. This is anticipated to occur approximately 18 months after the first participant is randomized into the study with approximately 49 and 107 deaths in ESR1 mutant and all participants population, respectively. OS will be tested in ESR1 mutant subgroup first with the allocated alpha (plus passed alpha from PFS testing per testing procedure if applicable) under group sequential trial design consideration with Lan-DeMets/O'Brien-Flemming boundary (O'Brien & Fleming, 1979). OS will be formally tested in all participants population only if OS testing in ESR1 mutant subgroup is positive. Otherwise, an administrative alpha spending (0.0000001) will be spent for OS IA1 analysis among all participants due to unblinded descriptive analyses and the study will proceed to the second OS interim analysis.

The second OS interim analysis (IA2) will be performed at 130 deaths in ESR1 mutant subgroup (approximately 67% of total 194 events required for the final analysis). This is anticipated to occur approximately 38 months after the first participant is randomized into the study. Following the same alpha spending principle as described in IA1, if OS IA2 is positive for ESR1 mutant subgroup, OS will be formally tested among all participants population per pre-specified testing procedure with available deaths events at the time (for example, approximately 265 deaths). Otherwise, OS for ITT will not be formally tested at IA2 and the study proceeds to the OS final analysis (396 events).

The analysis details will be documented and approved in the SAP.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blinding (if applicable) as per Pfizer's SOPs will be documented and approved in a(n) DMC charter. In addition, the analysis details will be documented and approved in the SAP.

9.5. Sample Size Determination

This is an international Phase 3 multicenter, randomized, open label, parallel-group study.

The study is designed to test the null hypothesis vs. the alternative hypothesis noted below in each of the two participant populations: 1) all randomized participants, and 2) participants with ESR1 mutation. The following statistical hypotheses will be tested to address the primary objective:

$H_{0\ \text{all participants}}$: $HR_{PFS} \geq 1$ vs $H_{1\ \text{all participants}}$: $HR_{PFS} < 1$

$H_{0\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{PFS} \geq 1$ vs $H_{1\ \text{ESR1 } mutant\ \text{participants}}$: $HR_{PFS} < 1$

For all participant population, approximately 560 participants (including approximately 280 ESR1 *mutan*t participants) will be randomly assigned on a 1:1 basis to:

- Arm A: ARV-471, Investigational Arm – n ≈ 280 or
- Arm B: fulvestrant Comparator Arm – n ≈ 280

Participants will be stratified by ESR1 mutational status (*Mutant*, Yes/No) and visceral disease (Yes/No).

The 1-sided α level of 1.875% was used for sample size calculation according to statistical hypothesis testing strategy.

For PFS in all participants population, based on a 1:1 randomization allocation ratio, a total of 310 PFS events will provide 92.5% power for a 1-sided log-rank test at a 0.01875 significance level to detect a HR < 0.67. For PFS in participants with ESR1 mutation, a total of 165 PFS events will provide 88% power for a 1-sided log-rank test at a 0.01875 significance level to detect a HR<0.60. It is estimated that approximately 560 participants will be needed to observe the 310 PFS events in all participants population, and out of which, approximately 280 ESR1 *mutant* participants are required to observe 165 PFS events in the subgroup population.

For OS, approximately 396 death events will provide 80% power for a 1-sided log-rank test at 0.025 significance level to detect a HR < 0.75 in all participants population; and 194 death events in ESR1 *mutant* population provides 80% power to test a HR <0.667 in ESR1 *mutant* population.
The sample size calculation is based on the following assumptions:

- The median PFS and OS for participants receiving fulvestrant are 4 months and 25 months, respectively.
- The median PFS for participants receiving ARV-471 is 6 months in overall randomized population, which corresponds to a HR of 0.67 under an exponential assumption; and the median PFS is 6.7 months in ESR1 *mutant* population, which corresponds to a HR of 0.60 under an exponential assumption.
- The median OS for participants receiving ARV-471 is 33.2 months in overall randomized population, which corresponds to a HR 0.75 under an exponential assumption; and the median OS is 37.5 months in ESR1 *mutant* population, which corresponds to a HR of 0.67 under an exponential assumption.
- Participant dropout rate of 10% in each arm by the 20th month for PFS.
- Participant dropout rate of 10% in each arm by the 40th month for OS.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

The investigator must ensure that each study participant or their 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 their legally authorized representative, must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or their legally authorized representative.

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

The investigator further must ensure that each study participant or their legally authorized representative, is fully informed about his or her right to access and correct their 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 their legally authorized representative, must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an External Data Monitoring Committee (E-DMC). The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities and investigators, as appropriate.

10.1.5.2. Steering Committee

A Global Steering Committee will be established at the program level for ARV-471. It will be responsible for providing scientific advice and medical input on the ongoing and future clinical development plans for ARV-471 in ER(+) breast cancer, including for this study.

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results

are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

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

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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 records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source document and its origin can be found in the Source Document Locator, 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 record) that supports the information entered in the CRF.

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

10.1.9. Use of Medical Records

In certain situations, sponsor review of redacted copies of participant medical records for very complex cases (eg, including radiographic testing results or a hospital discharge report to better assess some adverse events, etc) may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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

The investigator may initiate study-site closure at any time upon notification to the sponsor 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;
- Negative benefit/risk assessment.

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

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

10.1.11. Publication Policy

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

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

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed

confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

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

10.1.12. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

10.1.13. Transfer of Obligations Statement

Arvinas Estrogen Receptor, Inc. ("Arvinas") and Pfizer entered into a collaboration agreement dated as of 21 July 2021 to co-develop the compound ARV-471. CCI

[redacted]

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

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in Table 2 and Table 3.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively.

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.

Please refer to Table 2 and Table 3 for the frequency of each assessment.

Laboratory assessments
Hematology
Hemoglobin
Platelets
WBC
Absolute Neutrophils (or % as per local practice)
Chemistry
ALT
AST
Alkaline Phosphatase
Sodium
Potassium
Magnesium
Total Calcium
Total Bilirubin[a]
BUN or Urea
Serum Creatinine
eGFR as per 2021 CKD-EPI Equations (at screening only for eligibility)
Albumin
HbA1C (fasting)
Glucose (fasting)
Triglycerides (fasting)
Cholesterol (Total Cholesterol, LDL, HDL) (fasting)
Coagulation (only at screening)
aPTT
INR
PT
Additional Test
FSH test (at screening only) to confirm a postmenopausal status of female participants under the age of 60 and with cessation of regular menses for 12 consecutive months and with no alternative medical cause.
Other Tests
HBV, HCV and HIV at screening only if required by local regulations
Pregnancy Test
For WOCBP participants only. Serum pregnancy test (at screening). Following screening pregnancy tests (urine or serum) must have sensitivity of least 25 mIU/mL.

Laboratory assessments

a 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, prothrombin time /INR, and alkaline phosphatase.

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

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

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

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

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

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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 using the CT SAE Report Form or via PSSA 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/PSSA 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/PSSA for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form/PSSA 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 or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant 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 SAE) using the CT SAE Report Form and EDP Supplemental Form or PSSA;
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form or PSSA, 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 or PSSA.

- 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

GRADE	Clinical Description of Intensity
1	MILD AE
2	MODERATE AE
3	SEVERE AE
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 their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form/PSSA 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 information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eSAE or PSSA). • If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

- **Arm A**:

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 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.

- **Arm B:**
  - Refer to the Faslodex EU SmPC for fulvestrant contraception requirements.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion No. 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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

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

  OR

  - **Arm A:**
    - Is WOCBP who agrees to use a highly effective contraceptive method (failure rate of <1% per year), with low user dependency during the intervention period and for at least 30 days after the last dose of ARV-471,

which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention.

OR

- Is WOCBP who agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 30 days after the last dose of study ARV-471, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention.

- **Arm B**: Refer to the Faslodex EU SmPC for fulvestrant contraception requirements.

The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling a woman with an early, undetected pregnancy.

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 consecutive 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 with no alternative physiological (this includes drugs) or pathological cause.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. IUD. Hormone based IUD are NOT allowed
2. Bilateral tubal occlusion. (eg, bilateral tubal ligation)
3. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User-Dependent

Sexual abstinence

4. 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.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

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

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

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

- The samples will be retained as indicated:

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

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

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

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Screat increase. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated. Screat and reflex Scys values are needed to estimate the combined Screat-Scys eGFR calculation to ascertain whether eGFR change from baseline is comparable for 2021 CKD-EPI eGFR Screat-only and for 2021 CKD-EPI eGFR combined Screat plus Scys.

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

eGFR (mL/min/1.73m²)

2021 CKD-EPI Screat Only	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽ 0.7	N/A	$eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ⩽ 0.9	N/A	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$

(Inker et al, 2021)

10.7.3. Kidney Function Calculation Tool

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate formulae (see Section 10.7.2.) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Please note that investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are

expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

NCI CTCAE (2017) Criteria	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute Kidney Injury (AKI)	N/A	N/A	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
AKI: A disorder characterized by acute loss of kidney function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidneys), renal (kidney damage), or post-renal causes (ureteral or bladder outflow obstruction.					
Creatinine increased	>ULN to 1.5 x ULN	>1.5 to 3.0 x baseline OR >1.5 to 3.0 x ULN	>3.0 to 6.0 x baseline OR >3.0 to 6.0 x ULN	>6.0 x ULN	N/A
Chronic Kidney Disease (CKD)	eGFR ⩾60 to 89 mmL/min/1.73m²	eGFR 30 to 59 mL/min/1.73m²	eGFR 15 to 29 mL/min/1.73m²	eGFR <15 mL/min/1.73m² OR dialysis indicated	Death
Proteinuria	Proteinuria 1+ OR Proteinuria >0.5 to <1.0 g/24hr	Proteinuria 2+ or 3+ OR Proteinuria 1.0 to <3.5 g/24hr	Proteinuria 4+ OR Proteinuria ⩾ 3.5 g/24hr	N/A	N/A

CKD: A disorder characterized by gradual and usually permanent loss of kidney function resulting in kidney failure.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• New STT changes suggestive of myocardial ischemia.
• New onset LBBB (QRS complex >120 ms).
• New onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
  • Sustained supraventricular tachycardia (rate >120 bpm) (“sustained” = short duration with relevant symptoms or lasting >1 minute).
  • Ventricular rhythms >30 seconds’ duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm),

and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as Torsades de Pointes]).

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

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.9.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.9.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.2)
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition
• A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.9.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.9.4. Recording/Reporting and Follow-up of and Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency 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 device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and will also capture the required information on the Medical Device Complaint Form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms.

Device Deficiency Recording

Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3).

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. 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 product information in their assessment.
- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency
• The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency
• 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/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the CT SAE Report Form/PSSA within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.9.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

10.9.6. Reporting of SADES

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, a SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.10. Appendix 10: Concomitant Medications That May Result in DDI

10.10.1. CYP3A inhibitors/inducers.

The concurrent use of the following medications, food or herb supplements is **prohibited** throughout the duration of the active treatment phase.

- **ARV-471:** 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.

- **Fulvestrant**: No DDI is expected by the concomitant use with fulvestrant. Refer to Faslodex EU SmPC.

Prior use of medications, food or herb supplements that are strong inhibitors of CYP3A must be stopped 7 days before randomization. Strong inducers of CYP3A must be stopped 14 days before randomization.

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.

Drug Category	Drugs
Strong CYP3A inhibitors*	**Antibiotics**: clarithromycin, josamycin, telithromycin, troleandomycin **Antidepressants**: nefazodone **Antifungals**: itraconazole, ketoconazole, posaconazole, voriconazole **Antiprogestins**: mifepristone **Antivirals**: boceprevir, danoprevir, elvitegravir, ensitrelvir, indinavir, lopinavir, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir, telaprevir, tipranavir **Calcium channel blocker**: mibefradil **Pharmacokinetic enhancer**: cobicistat **Vasopressin antagonists**: conivaptan **Food products**: grapefruit, grapefruit juice or any product containing grapefruit **Farnesyltransferase inhibitor**: lonafarnib
Strong CYP3A inducers*	**Antibiotics**: rifampin, rifapentine **Anticonvulsants**: carbamazepine, phenytoin **Cystic fibrosis treatments**: lumacaftor **Herbal medications**: St. John's wort

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

- UW: https://www.druginteractionsolutions.org/
- FDA: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

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

Concurrent use of ARV-471 with drugs of known risk of causing Torsade de Pointes or QT interval prolongation is **prohibited** for the majority of the drugs listed in the table below. The concurrent use of fulvestrant with drugs of known risk of causing Torsade de Pointes or QT interval prolongation is also **prohibited**.

Exception: sevoflurane, azithromycin, ondansetron, chloroquine may be used **with caution** during the active treatment for all the participants with the exception of the participants in the QTc sub-study in Arm A for whom the use is **prohibited** during Cycles 1, 2 and Cycle 3.

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

Drug Category	Drugs
Drugs known to predispose to Torsade de Pointes	**Anesthetic**: sevoflurane[1], propofol **Antianginal**: bepridil **Antiarrhythmic**: ibutilide, dofetilide, dronedarone, flecainide, nifekalant, hydroquinidine, quinidine, disopyramide, amiodarone, sotalol, procainamide **Antibiotic**: azithromycin[1], ciprofloxacin, clarithromycin, erythromycin, gatifloxacin*, grepafloxacin*, levofloxacin, moxifloxacin, roxithromycin, sparfloxacin* **Antidepressant**: citalopram, escitalopram **Antiemetic**: domperidone, ondansetron[1] **Antifungal**: pentamidine, fluconazole **Antihistamine**: terfenadine*, astemizole* **Antilipemic**: probucol* **Antimalarial**: halofantrine, chloroquine[1], hydroxychloroquine **Antiparasitic**: meglumine antimoniate **Antipsychotic**: thioridazine, levomepromazine (methotrimeprazine), mesoridazine*, haloperidol, chlorprothixene, levosulpiride, pimozide **Antipsychotic/antiemetic**: chlorpromazine, droperidol, sertindole, sulpiride, sultopride **Cholinesterase inhibitor**: donepezil **GI stimulant**: cisapride* **Muscle relaxant**: terodiline **Opioid agonist**: methadone, levomethadyl acetate* **Phosphodiesterase 3 inhibitor**: anagrelide, cilostazol **Psychedelic**: ibogaine **Vasoconstrictor**: terlipressin **Vasodilator**: papaverine HCl (intra-coronary)

1 Allowed to be used with **caution** (per USPI and SmPC) during the active treatment for all the participants with the exception of the participants in the QTc sub-study in Arm A for whom the use is **prohibited** during Cycles 1, 2 and 3.
*Removed from US market

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 Torsades de Pointes (TdP) – Known Risk of TdP)".

See website for current list: crediblemeds.org/index.php/druglist

10.10.3. P-gp Sensitive Substrates

ARV-471 is an *in vitro* inhibitor of P-gp. Treatment with ARV-471 has potential for increasing exposure of concomitant medications that are sensitive substrates for P-gp transporters. Sensitive P-gp substrates should be used **with caution**.

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

Drug Category*	**Drugs**
P-gp sensitive substrates	**Anticoagulants**: dabigatran etexilate **Antiarrhythmics**: digoxin/digitoxin **Histamine H-1 receptor antagonists**: fexofenadine

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

- UW: https://www.druginteractionsolutions.org/
- FDA: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

No interaction with P-gp has been observed for fulvestrant.

10.10.4. PPI

Co-administration of PPIs may reduce ARV-471 absorption. The concomitant use of PPIs with ARV-471 is not recommended. If PPI treatment is required, drug intake with a moderate-fat meal (400-800 calories, approximately 35% fat) is recommended.

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

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

* Refer to corresponding concomitant drugs USPIs or local product prescribing information.

10.11. Appendix 11: Country Specific Requirements

10.11.1. European Union

This study will be conducted in compliance with Regulation (EU) No 536/2014. The recruitment plans for each EU Member State concerned are included in the respective Recruitment and Informed Consent Procedure documents.

The sponsor will notify EU Member States concerned of the following:

- Any SUSAR via reporting to the EudraVigilance database
- Any unexpected event that affects the benefit risk-profile of the study, but are not SUSARs, no later than 15 days of becoming aware of that event
- Any serious breach, as described in Section 10.1.1.1, no later than 7 days of becoming aware of that breach
- Any urgent safety measure, as described in Section 10.1.1.1, no later than 7 days of the measure being taken
- Any inspection report of a third-country authority concerning the study

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 25 years or longer if required by other European Union law.

10.11.2. France

Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

   No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

   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 ICH GCP that the investigator becomes aware of.

4. Termination Rights

   Pfizer retains the right to discontinue development of ARV-471 at any time.

10.12. Appendix 12: 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(Ellis, 1961)*

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**

10.13. Appendix 13: 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 (Eisenhauer et al, 2009)

CATEGORIZING LESIONS AT BASELINE

All sites of disease must be assessed at screening as close as possible to randomization date (≤ 28 days prior to randomization date as defined in the protocol unless otherwise specified in Section 8.2). If screening assessment is inadequate, subsequent statuses generally should be not evaluable.

Lesions are selected at screening and followed as either target or non-target lesions. All target lesions must be measurable. Any lesions or sites of disease not classified as target lesions including those that are non-measurable are classified as non-target. Definitions of measurable, non-measurable, target, and non-target lesions are provided below.

Measurable Lesions

Measurable lesions (including both nodal and non-nodal) are lesions that can be accurately measured as follows:

- Lesions with longest diameter ≥ 10 mm in the axial plane (bone lesions are not included except for soft tissue expansile masses arising from bone) when assessed by CT or MRI
- Lesions with longest diameter ≥ 20 mm when assessed by Chest X-ray
- Superficial lesions with longest diameter ≥ 10 mm when assessed by caliper
- Malignant lymph nodes with the short axis ≥ 15 mm. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the smaller of the axial, sagittal or coronal will be considered the short axis).

NOTE: 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.

Non-measurable disease

All other disease including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, 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, nodes with short axis ≥ 10 mm but < 15

mm, disease documented by indirect evidence only (eg, by lab values), or previously radiated lesions that have not progressed, are considered non-measurable.

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 (lesions with longest diameter for non-lymph nodes ≥ 10 mm and nodes with longest short axis ≥ 15 mm) and suitability for accurate repeated measurements. Measurements are recorded in mm and must be provided for target lesions.

Non-Target Lesions

All non-measurable lesions are non-target. All measurable lesions not identified as target lesions are also included as non-target lesions.

OBJECTIVE STATUS AT EACH EVALUATION

Response is assessed by the investigators, with objective status at each assessment recorded on the Investigator Overall Objective Tumor Assessment (IOTA) CRF.

Objective Status is to be recorded at each post-baseline evaluation.

Sites of disease should be assessed using the same technique as baseline, including consistent administration of contrast agents (see Section 8.2.1). If a change needs to be made the case should be discussed with the radiologist and the sponsor to determine if substitution is possible.

If target lesions were present at screening, screening sum of diameters is calculated as the total sum of the longest diameters for non-nodal lesions and short axis for nodal lesions. Sum of diameters at subsequent assessments can be calculated in the same manner using the same set of target lesions.

Response evaluation of target lesions

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

- **Partial Response:** At least a 30% decrease from baseline in the sum of diameters of all target lesions. The short diameter is used in the sum for nodal target lesions, while the longest diameter is used in the sum for non-nodal target lesions. All target lesions must be assessed.

- **Progressive Disease (PD)**: At least a 20% increase in the sum of diameters of target measurable lesions above nadir (smallest sum observed considering baseline and all assessments prior to the timepoint under evaluation), with a minimum absolute increase of 5 mm relative to nadir. If only a subset of target lesions is assessed, and the sum of the non-missing lesion diameters results in an increase of at least 5 mm and at least 20% above the nadir then the progression criteria will have been met.

- **Stable Disease (SD):** Does not qualify for CR, PR, PD. All target lesions must be assessed.

- **Not Evaluable (NE):** PD has not been documented, and at least one of the following is true:

    - one or more target lesions have not been assessed

    - assessment methods used were inconsistent with those used at baseline (unless considered "interchangeable")

    - one or more target lesions cannot be measured accurately unless due to being too small to measure

    - one or more target lesions were excised or irradiated and have not reappeared or increased.

General considerations on Response Evaluation of Target lesions:

- A target lesion that is irradiated or excised post-screening is no longer measurable and generally should be assessed as Not Evaluable. Increase or reappearance of such lesions should constitute progression.

- For lesions that become necrotic in the center, the longest diameter should still be used in the sum of diameters.

- Measurements for target lesions that become small should continue to be recorded;
    - if the lesion is considered to have disappeared, 0 mm should be recorded;

    - if a lesion is determined to be present but too small to measure (ie lesion less than 10 mm and exact measurement cannot be performed), the lesion status will indicate "too small to measure" and 5 mm will be used in the calculation of the sum of the diameters.

- If 2 target lesions coalesce, the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- If a subset of the target lesions identified at baseline were not measured post-baseline, the objective status of target lesions at the visit is Not Evaluable, unless the partial sum of diameters for the subset of target lesions assessed at the visit already meets the PD criteria, ie, at least 5 mm and 20% increase above the smallest sum of diameters observed, in which case the objective status of target lesions at the visit is PD.

- If a lesion disappears and reappears at a subsequent time point, it should continue to be measured. The participant's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions and previous response. For example, if the participant's tumor had reached a CR status and a non-lymph node target lesion reappeared, then the participant's response would be considered PD at the time of reappearance.

- In contrast, if the tumor status was a PR or SD and 1 lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response.

Response evaluation of non-target lesions

- **Complete Response (CR)/Absent:** Complete disappearance of all non-target lesions. All nodes must decrease to normal (short axis < 10 mm). All disease sites must be assessed.

- **Non-CR/Non-PD/Present without unequivocal progression:** Persistence of 1 or more non-target lesion(s).

- **Progressive Disease (PD)/Unequivocal progression**: Unequivocal progression of existing non-target lesions.

- **Not All Evaluated/Inevaluable:** Progression has not been documented and non-target lesions are not all assessable or disease assessed with inconsistent methods (unless considered "interchangeable"), or one or more target lesions were excised or irradiated and have not reappeared or increased.

Note: there is no standard RECIST method of using non-target disease assessments to determine unequivocal progression in non-target disease; by the nature of non-measurable disease, this is not possible. Unequivocal progression is based on clinical judgment.

New lesions evaluation criteria

- If a lesion is identified in a location not scanned previously, this will be considered progression of disease (new lesion).

- If a new lesion is equivocal at one assessment (classified as "Equivocal") and verified at the next, (classified as "Unequivocal"), the earlier date is used as the progression date.

Objective Response Status at each assessment

Assessment is based on the target and non-target lesions response as described above and in Table 8.

Table 8. Objective Response Status at Each Assessment for Participants with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD or not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
SD	Non-PD* or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

*Non-PD includes CR and Non-CR/Non-PD
** New lesions must be unequivocal
CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; NE = not evaluable.

Note: cases for which target disease is assessed as SD or better but non-target assessments are missing, must be reviewed carefully. By considering the whole sequence, it may be reasonable to assume missed non-target assessments were not progression.

For participants with only non-target disease Table 9 will be used.

Table 9. Objective Response Status at Each Assessment for Participants with Non-Target Disease Only

Non-Target Disease	New Lesions	Objective Status
CR/Absent	No	CR
Non-CR/Non-PD/Present without unequivocal progression	No	Non-CR/Non-PD
Not all evaluated/Inevaluable	No	NE
PD/Unequivocal progression	Yes or No	PD
Any	Yes*	PD

*New lesions must be unequivocal
CR = complete response; PD = progressive disease; NE = not evaluable.

Date of Response

If there are multiple scan dates associated with a tumor evaluation, ie, radiological assessments occur over a series of days rather than the same day, the earliest scan date associated with the evaluation will be used as the date of the assessment. The same convention should be used for the investigator assessment (IOTA CRF page).

Best Overall Response

The BOR will be assessed based on reported overall lesion responses at different evaluation time points from the randomization date until the first documentation of progressive disease PD. For CR and PR, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after randomization.

10.14. Appendix 14: Additional Study Assessments, Inventories, and Questionnaires

10.14.1. Patient-reported Outcomes Assessments

These questionnaires will be collected:

- EuroQol 5 Dimensions, 5-Level (EQ-5D-5L) and Visual Analog Scale (VAS)
- EORTC QLQ-C30
- EORTC QLQ-BR23 (female and male questionnaire versions)
- Brief Pain Inventory (BPI) short form
- Modified Brief Pain Inventory Short Form
- Pain medication usage
- Injection site pain
- Patient preference questionnaire

The EQ-5D-5L, is a 5-item participant-completed questionnaire designed to assess health status in terms of a single index value or utility score. There are 2 components, a Health State Profile which has individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a VAS in which participants rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction (Rabin & de Charro, 2001).

The EORTC QLQ-C30 is a well-known, validated and self-administered PRO. The EORTC QLQ-C30 is a 30-question survey, which can be grouped into 5 functional domain subscales, including a physical functioning subscale, a role functioning subscale, an emotional functioning subscale, a cognitive functioning subscale and a social functioning subscale. Higher scores on the functional domains are indicative of higher levels of functioning. Oncology related symptoms assessed by the EORTC QLQ-C30 include fatigue (3 items), pain (2 items), nausea and vomiting (2 items), and dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact (1 item each). Higher scores are reflective of a greater presence of symptoms (Aaronson et al, 1993).

The EORTC QLQ-BR23 (female and male versions) is a 23-item breast cancer-specific companion module to the EORTC QLQ-C30 and consists of four functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and four symptom scales (systemic side-effects, breast symptoms, arm symptoms, upset by hair loss). Like the QLQ-C30, higher scores represent a better level of functioning/QoL than lower scores on functional and global QoL scales. However, for symptom-oriented scales, higher scores

represent greater symptom severity (Sprangers et al, 1996). Female and male questionnaire versions will be used depending on participant's gender.

The BPI is one of the most widely used tools to assess clinical pain. There are two versions, the long and short form. The short-form version of the BPI will be used in C4891001 and consists of items intended to measure participant perceptions of pain severity, items to assess the degree of interference of pain on daily functioning, body diagrams on which participants indicate the location of pain, an item to record pain medication usage, and a visual analogue scale to assess the degree of pain relief in the last 24 hours. Items in the pain severity scale evaluate the participant's pain "at its worst", "at its least", and "on average" over the previous 24 hours, as well as "pain now" (at the time of assessment). Participants respond on a 10-point numerical rating scales, where 0 = "no pain" and 10 = "pain as bad as you can imagine". The pain interference scale asks participants to rate how their pain interferes with "enjoyment of life", "general activity", "walking ability", "mood", "sleep", "normal work" and "relations with other people." Responses for the interference scale are also based on 10-point numerical rating scale anchored by 0 = "does not interfere" and 10 = "interferes completely". Higher scores are indicative of higher levels of pain and the impact attributed to pain (Cleeland & Ryan, 1994). While the full BPI-SF will be assessed during each cycle for the first six cycles and followed by every other cycle thereafter, the item 3 and item 9a of the mBPI-SF will be collected daily for participants in Arms A & B. The item 3 of the mBPI-SF measures "worst pain in the last 24 hours" and the item 9a measures "pain interference with general activity in the last 24 hours. Injection site pain will be collected daily for participants in Arm B. Consumption of pain medication will also be collected daily for participants in Arms A & B

The patient preference questionnaire (Arm A and Arm B) is a 3-item instrument designed to measure patients' preference for a method of treatment administration (oral versus injectable). The response scale varies for each question. The first question inquires about the preferred method of administration with the following responses: oral, injectable, or no preference. The other two questions ask patients about the strength of preference (response options ranging from 'very strong' to 'not very strong') and rationale for their preferred method of administration (response options include a checklist of specific reasons derived from qualitative interviews). Items are assessed without the use of a specific recall period; however, the respondents are asked to reflect on their experience with both methods of administration (oral or injectable) and preference when completing the instrument.

10.14.2. Eastern Cooperative Oncology Group (ECOG) Performance

Grade	Description
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, ie, light housework, 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.

(Oken et al, 1982)

10.15. Appendix 15: Protocol Amendment History

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

Amendment 2 (24 May 2023)

Overall Rationale for the Amendment: The protocol was amended to add lipid tests due to new drug class safety information as well as to incorporate regulatory feedback from specific countries and to address participant experience and operational issues.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Periodic cholesterol and triglyceride laboratory testing has been added.	Recent elacestrant (ORSERDU) approved USPI includes dyslipidemia in the Sections of "Warning and Precautions" and "Adverse Reactions". The newly added lipid tests will support the characterization of these safety events for ARV-471 and support participant safety.	Section 1.3 Schedule of Activities (Table 2) Section 10.2 Appendix 2
The Inclusion Criterion #4 has been slightly modified. • Clarified the definition of adjuvant therapy to be counted as a line of therapy in advanced/metastatic setting • Clarified that only one line of CDK4/6 inhibitor is allowed in any setting.	To improve clarity.	Section 1.1 Synopsis, Section 5.1 Inclusion Criteria

Description of Change	Brief Rationale	Section # and Name
• Clarified that the most recent ET may be the endocrine treatment component of the CDK4/6 inhibitor line of therapy.		
Exclusion Criterion #9: • Added "elacestrant" as prior treatment not allowed. • Removed prior CDK4/6 inhibitor treatment in the neoadjuvant/adjuvant setting. • Clarified that other investigational agents (including novel ET, any SERDs, SERCAs, CERANs) are not allowed.	Elacestrant (oral SERD) was initially listed in the EC#9 as investigational novel endocrine therapy (ie, SERD, SERCA, CERAN) not allowed. Since elacestrant has been recently approved by the FDA this drug has been reported separately. The sentence related to prior CDK4/6 inhibitor treatment removed to avoid duplication; clarification already added in the Inclusion Criterion #4. The participants should not have received any other investigational drug including novel ET.	Section 1.1 Synopsis, Section 5.2 Exclusion Criteria
Non-substantial Modification(s)		
ClinicalTrials.gov ID has been added.	To provide the ClinicalTrials.gov ID	Cover page Section 1.1 Synopsis
Synopsis has been streamlined and some further details (e.g. assessments) added.	To align with Sponsor protocol template.	Section 1.1 Synopsis

Description of Change	Brief Rationale	Section # and Name
Clarified the timing for pre-screening and screening activities.	To improve clarity.	Section 1.3 Schedule of Activities (Table 1)
Added that ESR1 test will be performed using a next-generation sequencing [NGS] test that evaluates other genes in addition to ESR1 gene.	To improve clarity.	Section 1.3 Schedule of Activities (Table 1) Section 8.1.1. Pre-screening
Screening activities may be performed while awaiting ESR1 test results/approval of prior ESR1 status. Added a trigger of 280 participants enrolled in either ESR1 status for stopping and clarified the pause of one population in case of extreme imbalance in ESR1 status enrollment. Once this trigger/pause is reached, enrollment of that population will cease/pause and the Sponsor will reinstate the sequential pre-screening /screening procedure.	To accelerate the pre-screening and screening activities and allow participants to access study treatment more quickly, the screening period may be initiated while the ESR1 test result/approval of prior ESR1 result is pending.	Section 1.3 Schedule of Activities (Table 1) Section 4.1 Overall Design
Added that the in China pre-screening ctDNA samples may be also used for tumor molecular profile/ctDNA level and ctDNA burden if the participants are randomized in the trial.	Clarification added to support the use of ctDNA level and tumor molecular profile from prescreening ESR1 test. This is also a support from protocol for China HGRAC application.	Section 1.3 Schedule of Activities (Table 1) Section 8.1.1 Pre-screening Section 8.7.2. Blood Samples
Clarified that ctDNA C1D1 samples may also be used for potential development of the companion diagnostic.	ctDNA samples may also be used for CD_X development in case the ctDNA samples collected during the pre-screening	Section 1.3 Schedule of Activities (Table 1) Section 8.7.2. Blood Samples

Description of Change	Brief Rationale	Section # and Name
	period are insufficient quantities and/or missing in collection. Samples to be tested as per regulatory requirements.	
Clarified that electrolytes should be performed on C1D1 when ECG is done. Clarified that weight is collected at screening. Paper PROs may be available. However, paper PROs should only be utilized if the electronic versions (on the electronic PRO devices) are not available for use (eg, not received at the site or not approved for use yet by the ethics committee). Clarified which assessments may be done during the home health visits.	To improve clarity.	Section 1.3 Schedule of activities (Table 2)
Clarified that the daily questionnaires are collected in the evening using the "evening daily diary".	To improve clarity.	Section 1.1 Synopsis Section 1.3 Schedule of activities (Table 2) Section 4.1. Overall Design Section 8.9. Health Economics Section 9.3.3.2.3. PRO data analyses
The time window for ECG and PK sample collected has been extended up to 2.5 hours prior to dose.	To give more flexibility since performing all assessments in a more restricted time window may be challenging.	Section 1.3 Schedule of activities (Table 3)
Clarified that ECG at screening should be done without fasting condition.	Fasting condition is not applicable in the screening period because required only starting from C1D1	Section 1.3 Schedule of activities (Table 3) Section 8.3.3 Electrocardiograms

Description of Change	Brief Rationale	Section # and Name
	for participants belonging to the QTc Substudy in Arm A.	
Benefit/Risk assessment text for QT prolongation slightly modified. Risks for decentralized/telehealth interactions study assessments added.	To improve clarity and to align with Sponsor protocol template.	2.3. Benefit/Risk Assessment
Added a text description of the estimand corresponding to the primary and key secondary objective and removed the statistical reference section.	To align with Sponsor protocol template.	Section 1.1 Synopsis Section 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS
LHRH may be provided by the Sponsor if available to source in-country.	To clarify that LHRH may be provided by the Sponsor in certain circumstances.	Section 6.9.1. Luteinizing Hormone-Releasing Hormone Agonist
Corticosteroids use has been added.	Limitation of the use of corticosteroids added for consistency with the EC#2.	Section 6.9.8 Corticosteroids
Updates have been added to align with Sponsor new protocol template.	To align with Sponsor protocol template.	Section 1.1 Synopsis Section 6.8. Treatment of Overdose Section 8.3.5. Pregnancy Testing Section 8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting Section 9.2 Analysis Sets Section 10.1 Appendix 1 Regulatory, Ethical, and Study Oversight Considerations Section 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting

Description of Change	Brief Rationale	Section # and Name
		Section 10.4.3. Woman of Childbearing Potential Section 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow Up Assessments and Study Intervention Rechallenge Guidelines Section 10.7. Appendix 7: Kidney Safety Monitoring Guidelines Section 10.8. Appendix 8: ECG Findings of Potential Clinical Concern Section 10.9. Appendix 9: AEs, ADEs, SAEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies
Clarification provided on home heath visits to be performed by a registered nurse/other qualified health care provider or by the investigator or a physician designee for specific assessments (if required by local regulations).	Clarification added as per Health Authorities requirement.	Section 8.1.4. Home Health Visits
For China: Clarified that Retained Research samples for genetics will not be collected and that sample collection for biomarkers and biomarker testing will be performed upon approval by HGRAC.	Clarification added as the collection of retained research samples will not be permitted by China HGRAC and will not be applied for HGRAC. Moreover, this clarification also emphasizes that the collection and analysis of biomarker samples must be applied after HGRAC approval; before that, no sample collection and	Section 8.6.2 Retained Research Samples for Genetics Section 8.7 Biomarkers

Description of Change	Brief Rationale	Section # and Name
	analysis should be applied in China.	
Updated population definition.	Simplified the definition of study population to avoid potential confusion.	Section 9.1.1. Estimands
Added a supplemental analysis for the primary endpoint PFS.	Requested by Health Authority.	Section 9.3.2 Primary endpoint analyses
For the PRO analysis, change from baseline and deterioration will be based on clinically meaningful threshold for the scale being examined.	To add further clarification.	Section 9.3.3.2.3. PRO data analyses
Added the reference of the methodology of group sequential Hochberg procedure for testing of OS in the two populations.	To add further clarification as requested by Health Authorities.	Section 9.4. Interim Analysis
Japan-specific section removed.	The device-related incident whose recurrence might lead to death or serious deterioration in health are not required to be reported as per local laws based on the discussion with PMDA. Fulvestrant is administered using pre-filled syringe (medical device) whereas the investigation drug ARV-471 does not contain any medical device. As per local law the device-related incident should be submitted to PMDA only in case fulvestrant contains the same medical device used in the investigational drug.	Section 10.11.2. Japan

Description of Change	Brief Rationale	Section # and Name
Typographical errors were corrected, and minor edits were made.	For clarification and to ensure consistency.	Section 4.2. Scientific Rationale for Study Design Table 6 "Recommended Dose Modifications for ARV-471 Related Toxicity" Table 7 "Recommended ARV-471 Dose Modification in the event of QTc Prolongation" Section 6.8. Treatment of Overdose status. Section 8.1.4. Home Health Visits Section 8.2.1 Imaging Tumor Response Assessments Section 4.2. Scientific Rationale for Study Design Section 10.14. Appendix 14: Additional Study Assessments, Inventories, and Questionnaires Section 10.16. Appendix 16: Abbreviations Section 11. REFERENCES
List of CYP3A inhibitors has been updated.	To provide a more exhaustive list of drugs that are known to be CYP3A inhibitors.	Section 10.10. Appendix 10: Concomitant Medications That May Result in DDI
Sponsor Legal Addresses have been added. This change incorporates the PACL dated 04 April 2023.	To align with Sponsor protocol template and as requested by Health Authorities.	Cover page
HBV, HCV, HIV laboratory testing has been added.	Tests added as per Health Authorities request and to be performed at screening	Section 1.3 Schedule of activities (Table 2) and Section 10.2 Appendix 2.

Description of Change	Brief Rationale	Section # and Name
This change incorporates the PACL dated 18 April 2023.	only if mandated by Regulatory Agencies.	

Amendment 1 (25 October 2022)

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

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Section 1.1 Synopsis, Section 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS, Section 4.1, Overall design, Section 8.2. Efficacy Assessments Section 9. STATISTICAL CONSIDERATIONS	PFS, tumor control and DOR between treatment arms will now be determined by BICR assessment. BICR will review all radiological images, clinical assessment of superficial lesions and clinical information (as applicable). The sensitivity analyses to support the primary analyses will be performed from local radiologist's /investigator's tumor assessment.	Health Authorities feedback recommended the primary end point (PFS) assessed by BICR due to the unblinded study.	Substantial
Section 1.1 Synopsis, Section 1.3 Table 2, Section 4.1. Overall Design, Section 8.9. Health Economics, Section 9.3.3.2.3. PRO data analyses	The frequency of the PRO assessment has been increased and mBPI-SF (worst pain severity and pain interference), injection site pain, pain medication usage via analgesic log and	Per Health Authorities feedback the frequency of the PRO assessment has been increased and additional questionnaires	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Section 10.14.1. Patient-reported Outcomes Assessments	patient preference questionnaires have been added.	have been added to potentially support labeling of PRO outcomes.	
Section 1.1, Synopsis, Section 1.3 Table 1 SoA prescreening Section 4.1, Overall design Section 5.1 Inclusion criteria	Removed requirement of approximately 80% of participants treated with prior CDK4/6 inhibitor and removed capping of approximately 20% for naïve participants. Updated IC#4 to mandate prior treatment with CDK4/6 inhibitor in combination with endocrine therapy and ≤ 1 additional endocrine therapy.	Health Authorities feedback requires that all participants should additionally receive a CDK4/6 inhibitor if not used previously according to guidelines. Since in this study no combination arm with CDK4/6 inhibitor is planned, the eligibility criteria have been modified and all participants should have been previously treated with CDK4/6 inhibitor.	Substantial
Section 1.3, Schedule of Activities, Table 1 Section 8.1.1 Pre-screening	Updated the total number of ctDNA samples.	For all participants, one addition sample is required for potential companion diagnostic development	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Section 1.3, Schedule of Activities, Table 2 Section 8.3.5, Pregnancy Testing Section 10.2 Appendix 2, Clinical Laboratory Assessments	Updated text on frequency of pregnancy tests requested for WOCBP.	To align with the LHRH product information in contraception and pregnancy tests for WOCBP due to the lack of effectiveness of LHRH agonist use to prevent pregnancy.	Substantial
Section 1.1, Synopsis, Schema Section 4.1, Overall design Section 6.3. Assignment to Study Intervention Section 9. Statistical Consideration	Modified the randomization from 2:1 to 1:1 and updated the total number of participants in the study and in each arm. Consequently, the number of statistical events has been updated.	Randomization has been changed as per consultation with regulatory agencies.	Substantial
Section 1.1 Synopsis Section 1.3, Schedule of Activities, Table 2 Section 4.2.3, Choice of Contraception/ Barrier Requirements Section 5.1 Inclusion criteria. Section 8.1.2 Telehealth Visits Section 8.1.3 Home Health Visits Section 10.4 Appendix 4: Contraceptive and Barrier Guidance	Updated text to specify that contraception & compliance checks are required for WOCBP and male participants. IC#1 was updated accordingly.	Based on LHRH agonist prescribing information (eg, USPI Zoladex), an LHRH agonist must be associated with the use of non-hormonal contraception.	Substantial
Section 1.1 Synopsis Section 5.2 Exclusion criteria	Updated EC #13: Renal impairment is defined as eGFR <45 mL/min/1.73m^2 as	Health authorities require the use of eGFR equation	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
	calculated using the 2021 CKD-EPI Equations. Serum creatine of >1.5 x ULN has been removed.	because is more inclusive and the most reliable overall index of kidney function. eGFR cutoff set to 45 mL/min/1.73m2 since renal clearance of ARV-471 is low.	
Section 1.1 Synopsis, Section 4.1 Overall design Section 6.3. Assignment to Study Intervention Section 9. Statistical Consideration.	Removed stratification factor for prior treatment with CDK4/6 inhibitor.	The stratification factor has been removed because participants must now be previously treated with a CDK4/6 inhibitor to be eligible.	Substantial
Section 1.1 Synopsis Table 3, Pharmacokinetic and ECGs Section 4.1 Overall design Section 8.3.3. Electrocardiograms Section 9.2 Analysis Sets Section 9.3.3.2.2. Pharmacokinetic Analysis Section 9.3.3.2.5.3. Summary and Categorical Analysis of ECG	Modified QTc study design and updated the total number of participants from approximately 60 to approximately 80 participants (from approximately 50 evaluable participants to approximately 60 evaluable participants). ECG and PK samples: the time points in the Arm A QTc sub-study has been reduced. ECG on C1D1 is mandatory for all participants.	Health Authorities agreed to a revised QT Sub-study design based on estimation of effect size in lieu of the hypothesis testing for non-inferiority. The new sample size calculation is based on new data from Study ARV-471-mBC-101 and the revised QTc	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
		Sub-study design.	
Section 1.1, Synopsis	Updated safety text	To align with updated IB	Substantial
Section 2.2.3, ARV-471	Added details on anti-tumor activity of ARV-471.	To align with updated IB	Substantial
Section 2.2.3.1, Nonclinical Pharmacokinetics and Metabolism	Added details on ARV-471 and on CYP metabolism and doses administered in dogs to measure exposure of ARV-471	To align with updated IB	Substantial
Section 2.2.3.2, Potential Drug- Drug Interaction Section 10.10.3, P-gp Sensitive Substrates	Updated text about impact of ARV-471 on CYP2B6 substrates and substrates of human transporters (P-gp and BCRP) and effect of PPI on ARV-471. Updated text for the use of antacids and H2 receptor antagonist.	To align with updated IB	Substantial
Section 2.2.3.3, ARV-471 Preliminary Safety, Efficacy and PK in Humans	Updated safety, efficacy and PK data based on study ARV-471-mBC-101 and ARV 471-CPhm-103.	To align with updated IB	Substantial
Section 2.2.3.4 QTc Evaluation Data. Section 10.10.2, Drugs Known to Predispose to Torsade de Pointes or QT interval prolongation	Updated safety data in non-clinical and clinical studies including concentration-QTc modeling analysis of data from the ongoing ARV-471-mBC-101 study.	To align with updated IB	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Section 2.3.1, Risk Assessment	Updated text about QTc prolongation and Venous embolism	To align with updated IB	Substantial
Section 2.3.2, Benefit assessment Section 2.3.3, Overall Benefit/Risk conclusion	Updated text about efficacy data based on study ARV-471-mBC-101.	To align with updated IB	Substantial
Section 4.3.1. ARV-471	Updated safety, efficacy and QTc data.	To align with updated IB	Substantial
Section 1.1, Synopsis Section 1.3, Schedule of Activities, Table 2 Section 4.1, Overall Design Section 5.1 Inclusion Criteria Section 6.9.1 Luteinizing Hormone-Releasing Hormone Agonist	Updated text on LHRH initiation and to allow participants already on treatment with every 3-month formulation to continue it. IC#1 updated accordingly.	To align with NCCN Breast Cancer guidelines.	Substantial
Section 6.9.3. Other Prohibited and/or Anti-Cancer or Experimental Drugs, or Procedures Section 10.10.2. Drugs Known to Predispose to Torsade de Pointes or QT interval prolongation	The use of sevoflurane, azithromycin, ondansetron, chloroquine has been prohibited during Cycle 3 for the participants in the QTc-Substudy in Arm A.	To align with the modified QTc study design as per Section 9.3.3.2.5.3.1. Electrocardiogram Analyses for QTc Analysis Set	Substantial
Section 6.9.4 Concomitant Treatments to be used with Caution or Not Recommended	Updated details with reference to the use of H2 receptor antagonists and local antacids.	To align with updated IB	Substantial
Schedule of Activities, Table 2	Added weight collection on Day 1 of each cycle and at EOT. Clarified that height is collected at screening.	To monitor the impact of endocrine therapy on body weight.	Substantial
Section 1.1, Synopsis	Added description of the program level	For added clarity.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Section 4.1, Overall Design and Section 10.1.5.2. Steering Committee	Global Steering Committee		
Section 1.1, Synopsis Section 1.3, Schedule of Activities, Table 2 Section 4.1 Overall Design Section 8.9 Health Economics Section 9.3.3.2.3. PRO data analyses Section 10.14. Appendix 14	Added clarification on EORTC QLQ-BR23 questionnaire for which female and male versions are available.	To clarify that EORTC QLQ-BR23 questionnaire female and male versions will be analyzed separately.	Non-substantial
Section 1.3, Schedule of Activities, Table 2 Notes Column	Updated text about C1D1 time window, sequence of assessments and bone scan at the EOT.	To add clarity	Non-Substantial
Section 1.3, Schedule of Activities, Table 2 Section 8.2.1. Imaging Tumor Response Assessments Section 8.2.1.1. Treatment Beyond Progression in Both Arms	Removed recommended PD confirmation.	PD confirmation not required by RECIST v1.1	Non-substantial
Section 1.3, Schedule of Activities, Table 2 Section 6.5 Study Intervention Compliance	Updated text clarifying that compliance will be assessed prior to the dispensing of study interventions	The language related to the drug compliance has been aligned with the sponsor protocol template.	Non-substantial
Section 1.3, Schedule of Activities, Table 2 Section 8.2.1. Imaging Tumor Response Assessments	The frequency of the tumor assessment has been clarified to be every 8 weeks for the first 48 weeks.	To add clarity.	Non-substantial
Schedule of activities (Table 3) and Section 8.3.3. Electrocardiograms	Updated timing of PK sample collection and	The timing has been restricted to 5-7 h to align	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
	central reading requirements	with expected T_{max} and central reading is not required at screening because ECG is only for eligibility evaluation.	
Section 1.3, Schedule of Activities, Table 2 & Table 3 Section 6.1.1.1 ARV-471 Section 6.1.1.2. Fulvestrant Section 6.2. Preparation, Handling, Storage, and Accountability Section 6.2.1. Preparation and Dispensing Section 6.5. Study Intervention Compliance Section 7.1.1.1. Safety Follow-up Section 8.1.2. Telehealth Visits Section 8.1.3. Home Health Visits Section 8.5. Pharmacokinetics Section 8.9. Health Economics	In case of home health visit the participant will not return to the site. Therefore, the paragraphs have been updated to accommodate home health activities. A more detailed list of assessments to be performed during home health visit has been added.	The language has been slightly modified to accommodate home health visits.	Non-substantial
Table 7 ARV-471 Dose Modification in the event of QTc Prolongation	The recommended dose modifications in case of QTc prolongation (with no reversible cause identified) have been revised.	The recommended dose modifications have been updated for consistency with the retreatment parameters reported in the	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
		Section 6.6.2.5 ARV-471 Dose Delays.	
Section 7.1. Discontinuation of Study Intervention Section 8.2.1.1. Treatment Beyond Progression in Both Arms	Clarified that objective disease progression is assessed by Investigator in case of discontinuation and for treatment beyond progression. Added request of participant's consent for treatment beyond progression	To add clarity	Non-substantial
Section 8.1.1 Pre-Screening	Added reference to Table 1 and additional details related to pre-screening.	To add clarity	Non-Substantial
Section 8.2.1.4. Alternative Facilities for Tumor Assessment Section 8.3.3.1. Alternative Facilities for Electrocardiograms	Tumor assessment and ECG (unscheduled ECGs done as clinically indicated) can be performed at alternative facilities if approved upon written notification from the sponsor.	To align with the Section 8.1.5. Alternative Facilities	Non-Substantial
Section 8.3.3. Electrocardiograms	Clarified that ECG interval readings will be read and interpreted at the site for eligibility determination and safety monitoring and clarified that ECG tracing should be sent to storage/analysis to the external vendor.	To add clarity	Non-Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Non-substantial
Throughout the protocol	Typographical errors and minor edits were made.	For clarification and to ensure consistency	Non-Substantial

10.16. Appendix 16: Abbreviations

Abbreviation	Term
aBC	advanced breast cancer
ADE	adverse device effect
AE	adverse event
AESI	adverse events of special interest
AI	aromatase inhibitors
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
AKT	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{tau}	area under the concentration-time curve during the dosing interval (τ)
AV	atrioventricular
AxMP	auxiliary medical products
BC	breast cancer
BCRP	breast cancer resistance protein
BCS	biopharmaceutics classification system
BICR	blinded independent central review
BID	twice daily
BOR	best overall response
BP	blood pressure
BPI	brief pain inventory
BPI-SF	brief pain inventory short form
bpm	beats per minute
BUN	blood urea nitrogen
C	cycle
CAP	chest, abdomen and pelvis; College of American Pathologists
CBR	clinical benefit response
CDK4/6	cyclin dependent kinase 4/6

Abbreviation	Term
CERAN	complete estrogen receptor antagonist
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology collaboration
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
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
CT	computed tomography; clinical trial; chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTIS	clinical trial information system
CV	cardiovascular
CYP	cytochrome
CYP2B6	cytochrome P450 2B6
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
D	Day
DCT	data collection tool
DDI	drug-drug interaction
DIDB	drug interaction database
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DU	dispensable unit
EC	ethics committee; exclusion criteria
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCrCl	estimated creatine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	external data monitoring committee
EDP	exposure during pregnancy

Abbreviation	Term
eGFR	estimated glomerular filtration rate
EORTC QLQ-BR23	European Organization for the Research and Treatment of Cancer and Quality of Life Questionnaire-Breast Cancer specific
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer and Quality of Life Questionnaire
EOT	end of treatment
EQ-5D-5L	European quality of life five-dimension five-level scale
EMA	European Medicines Agency
ER	estrogen receptor
ERα	estrogen receptor alpha
ESR1	estrogen receptor 1
ET	endocrine therapy
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FIH	first in human
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
FU	follow-up
g	gram
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GMCSF	granulocyte macrophage colony stimulating factor
H2	histamine receptor 2
HbA1C	hemoglobin A1c
HBV	hepatitis B virus
HCl	Hydrochloride acid
HCP	health care professional
HCV	hepatitis C virus
HDL	high-density lipoprotein
hERG	human ether-a-go-go related gene
HER2	human epidermal growth factor receptor 2
HGRAC	Human Genetics Resources Administration of China
HIV	human immunodeficiency virus
HR	heart rate; hazard ratio
IA	Interim Analysis
IB	Investigator's Brochure
IC	Inclusion Criteria

Abbreviation	Term
IC_{50}	inhibitory concentration 50
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	immuno-histochemistry
ID	identification
IM	intra-muscular
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IoR	Importer of Record
IOTA	investigator overall objective tumor assessment
IPM	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intent -to-treat
IUD	intrauterine device
IV	intravenous
IWR	Interactive Web-based Response
K2 EDTA	dipotassium ethylenediaminetetraacetic acid
kg	kilogram
LBBB	left bundle branch block
LDL	low-density lipoprotein
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LLN	lower limit of normal
mBC	metastatic breast cancer
mBPI-SF	modified brief pain inventory short form
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MID	minimally important difference
mIU	milli-international unit
ml	milliliter
mm	millimeter
MMRM	mixed model repeated measures
mPFS	median progression free survival
MQI	medically qualified individual
MRI	magnetic resonance imaging
msec	millisecond
mTOR	mammalian target of rapamycin

Abbreviation	Term
N/A	not applicable or not available depending on the context
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
n or N	number
NGS	Next-Generation Sequencing
NIMP	non-investigational medicinal product
OR	objective response
ORR	objective response rate
OS	overall survival
PARP	poly adenosine diphosphate-ribose polymerase
PACL	protocol administrative change letter
PD	pharmacodynamics(s) or progression of disease depending on the context
PE	physical examination
PFS	progression-free survival
P-gp	P-glycoprotein
pH	potential of hydrogen
PI	principal investigator
PI3K	phosphoinositide-3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PLT	platelet
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	proton pump inhibitors
PR	partial response
PRO	patient-reported outcomes
PROTAC	PROteolysis Targeting Chimeric
PS	performance status
PSSA	Pfizer's Serious AE Submission Assistant
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	corrected QT (Fridericia method)
QTcS	corrected QT (Study specific)
QTL	quality tolerance limit
RANKL	receptor activator of nuclear factor kappa-B ligand
rBA	relative bioavailability
RBC	red blood cell

Abbreviation	Term
RCI	repeated confidence interval
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
RP3D	recommended phase 3 dose
SABCS	San Antonio Breast Cancer Symposium
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Screat	serum creatinine
Scys	serum cystatin C
SD	stable disease
SERCA	selective estrogen receptor covalent antagonist
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulator
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SSID	single subject identifier
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	terminal elimination half-life
T bili	total bilirubin
Tdp	Torsades de Pointes
TEAE	treatment-emergent adverse events
TGI	tumor growth inhibition
TK	toxicokinetics
T_{max}	time to maximum concentration
TOC	table of contents
TRAE	treatment related adverse events
TTD	time to deterioration
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United State Package Insert
UW	University of Washington
VAS	visual analog scale
VE	venous embolism
VS	versus
WBC	white blood cell

Abbreviation	Term
WOCBP	woman/women of childbearing potential
WT	wild-type

11. REFERENCES

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