An Open-Label, Randomized, Non-Comparative Phase 2 Study of ARV-471 or Anastrozole in Post-Menopausal Women With ER+/HER2– Breast Cancer in the Neoadjuvant Setting

Protocol Number:	ARV-471-BC-201
Study Intervention Number:	ARV-471 (PF-07850327)
Study Intervention Name:	NA
Phase:	2
US IND Number:	140264
EudraCT Number:	2021-005081-17

Brief Title: A Phase 2 neoadjuvant study of ARV-471 and anastrozole

Sponsor Name:	Arvinas Estrogen Receptor, Inc (Arvinas)
Legal Registered Address:	5 Science Park, 395 Winchester Ave, New Haven, CT 06510
Date of Original Protocol:	27 May 2022
Date of Global Amendment #1:	09 Jan 2023

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DOCUMENT HISTORY

Document	Date of Issue
Original protocol	27 May 2022
[redacted] Amendment to Original Protocol	14 Dec 2022
Global Amendment #1	09 Jan 2023

Protocol Amendment Summary of Key Changes Table

Global Amendment #1 (09-JAN-2023)

Overall Rationale for the Amendment: To align the protocol with the most current version of the Investigator's Brochure, [redacted], add mRECIST, and further clarify some operational aspects of the study.

Substantial Amendment: No

Section # and Name	Description of Key Changes	Brief Rationale
1.1 Synopsis and throughout	Surgical resection accepted C6D18 ± 14 days instead of C6D18 ± 10 days	To allow the sites more flexibility in scheduling of surgery.
1.1 Synopsis	Inclusion clarified to participants for whom neoadjuvant endocrine monotherapy is deemed appropriate	Study population further clarified [redacted]
1.1 Synopsis	Addition to exclusion criteria #7 to exclude patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.	Included further detail on population of patients that should be excluded from study [redacted]
1.3 Schedule of Activities	ECG may be performed on site or vendor machines	To allow the sites to use the vendor ECG machine in screening if available.
1.3 Schedule of Activities	If screening ECG is used for C1D1, it must be done in triplicate and on a vendor machine	Clarification of the process for substitution of screening for C1D1 ECGs at baseline.
2.2.1.1.3 Nonclinical Pharmacokinetics and Drug-Drug Interactions	Removed language that indicated PPIs are allowed and added details to Section 6.8.1.1 indicating that PPIs are not recommended.	To align section with the most current version of the Investigator's Brochure (version 4.0).
2.2.1.2 Anastrozole	Addition of suggestion for bone mineral density testing	Added language regarding bone mineral density from the anastrozole SmPC [redacted]
4.3.1 ARV-471	Additional information provided regarding suggested ARV-471 dose	To align section with more current data to support dose selection.

Section # and Name	Description of Key Changes	Brief Rationale
5.1 Inclusion Criteria	Inclusion clarified to participants for whom neoadjuvant endocrine monotherapy is deemed appropriate	Study population further clarified [redacted]
5.2 Exclusion Criteria	Addition to exclusion criteria #7 to exclude patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.	Included further detail on population of patients that should be excluded from study [redacted]
6 Study Intervention(s) and Concomitant Therapy	Bulk bottle supply language removed from Table 4	Bulk bottles will no longer be used in this study.
6.1.1 Administration	Study drug may be continued beyond C6D18 + 14 days if surgical resection is delayed for non-study related reasons and after discussion with medical monitor.	To allow patients to continue dosing study drug beyond C6D18 + 14 days after discussion with medical monitor.
6.5.1 ARV-471	Clarification in footnotes in Table 6 that only one dose re-escalation is permitted.	Clarification that only one dose re-escalation of ARV-471 will be allowed.
6.8 Prior and Concomitant Therapy	Additional detail added regarding herbal supplements and concomitant medications. Herbal supplements are not recommended. Other concomitant medications may be considered on a case-by-case basis.	Given potential for interactions with herbal supplements, language added indicating they are not recommended on study.
6.8.1.1 ARV-471	Details added regarding co-administration of PPIs and H2 blockers. The concomitant use of PPIs with ARV-471 is not recommended. H2 blockers (eg, cimetidine, famotidine) or local antacids (eg, aluminum hydroxide, calcium carbonate, bismuth subsalicylate) may be used.	To align concomitant medications section with the most current version of the Investigator's Brochure (version 4.0).
6.8.1.3 Other Prohibited and/or Limited use of Anti-tumor/Anti-Cancer or Experimental Drugs, or Procedures	Clarification added for therapies with known anti-cancer effects	Clarification that the on-study prohibition of anti-cancer therapies is limited to the time prior to surgical resection.
6.8.2 Other Restrictions and Precautions	Clarification added for participation in any other interventional or non-interventional studies	To allow for prospective evaluation of participation in any other investigational study by medical monitor.
8.1.1.2 Radiographic Imaging Assessment	Added MRI as preferred imaging modality	RECIST 1.1 guidelines specify that MRI is the preferred imaging modality to follow breast lesions in the neoadjuvant setting.
8.1.1.2 Radiographic Imaging Assessment	Modifications made to include modified RECIST 1.1 (see also Appendix 11)	Clarification that mRECIST will be used to define response.

Section # and Name	Description of Key Changes	Brief Rationale
8.2.3 Electrocardiograms	Clarification that if screening ECG is obtained on a vendor machine within 96 hours of C1D1 in triplicates, there is no need to repeat the pre-dose ECG testing on C1D1. Details added regarding collection of ECGs. All triplicate ECG tracings will be sent electronically to a central ECG laboratory for manual interval measurements. All ECG's must be reviewed by qualified personnel at the site. If vendor ECG machine readings return an abnormal ECG finding, the investigator may use their site machine to repeat the assessment.	Clarification on the process for collecting ECGs and interactions with central ECG vendor.
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Addition of definition of last administration of study intervention as study drug treatment of surgical resection, whichever comes last.	Clarify meaning of last administration of study intervention.
8.3.1.2 Recording Nonserious AEs and SAEs on the CRF	Clarification that the recording of non-serious AEs and SAEs will continue until 30 days after last administration of study intervention.	Clarification as to when recording of non-serious AEs and SAEs will stop.
9.3.1 General Considerations	Clarification that CIs will be two-sided.	Stats clarification.
9.3.3 Secondary Endpoint(s)/Estimands Analysis	Clarification that radiographic response will be evaluated per mRECIST.	To align evaluation with addition of Appendix 11.
10.11 Appendix 11: Radiological Imaging Assessment: modified Requirements and RECIST 1.1	Addition of Appendix 11 to describe modified RECIST 1.1	Clarification on definition of mRECIST for this trial.

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Arvinas Estrogen Receptor, Inc. (Arvinas)

Name of Investigational Product(s): ARV-471 and anastrozole

Title of Study: An open-label, randomized, non-comparative Phase 2 study of ARV-471 or anastrozole in post-menopausal women with ER+/HER2– breast cancer in the neoadjuvant setting

Study Centers: Multicenter, global [US, Germany, Georgia, and Spain]

Phase of Development: Phase 2

Objectives, Endpoints and Estimands:

Objective	Endpoints
Primary	
Evaluate the effects of ARV-471 and anastrozole, respectively, on Ki-67 expression in tumors after 2 weeks of treatment	Percent change in Ki-67 expression between baseline and C1D15 tumor biopsies Estimand: See Section 9.1.2.1.
Secondary	
Evaluate the safety and tolerability of ARV-471 and anastrozole, respectively	Incidence of all adverse events, serious adverse events, and adverse events leading to study drug discontinuation
Evaluate the clinical and pathological response of ARV-471 and anastrozole, respectively	Pathologic stage, pathologic complete response (pCR) rate, and modified Pre-operative Endocrine Prognostic Index (mPEPI) score at the time of surgical resection (C6D18 ± 14 days); rates of breast conserving surgery (BCS); radiographic response of the primary tumor based on breast imaging during cycle 6; caliper-based response on C6D1
Exploratory	
Evaluate the effects of ARV-471 and anastrozole, respectively, on CCCA after 2 weeks of treatment	CCCA (Ki-67 ≤2.7%) rates at C1D15
Evaluate ER degradation by ARV-471	Percent change in ER protein levels between baseline and C1D15
Evaluate the effects of ARV-471 and anastrozole, respectively, on Ki-67, and ER degradation by ARV-471 in tumors at the time of surgical resection	Changes in ER and Ki-67 expression between baseline and Cycle 6 surgical tumor samples; Rates of CCCA in the Cycle 6 surgical samples
Explore additional biomarkers that may be associated with the effects of ARV-471 in tumor tissue	Additional biomarkers may include, but are not limited to, PgR expression, [redacted]
Correlate exposure of ARV-471 with ER reduction	Correlate population PK model-derived PK parameters (AUC, C_{min}, C_{max}) with ER reduction or other response parameters

Rationale/Overall Study Design:
Clinical trials evaluating pre-operative endocrine therapy in hormone receptor positive (HR+) human epidermal growth factor receptor 2 negative (HER2–) breast cancer allow for rapid assessment of novel therapeutic approaches (Guerrero-Zotano 2017; Denduluri 2018). Several trials evaluating pre-operative endocrine therapy have focused on biologic endpoints in tumor samples. In particular, Ki-67 has been used as a biomarker to assess the activity of ER-targeting agents, and Ki-67 results in the neoadjuvant setting may correlate with outcomes in the adjuvant or metastatic setting (Guerrero-Zotano 2017).

This trial is a Phase 2 neoadjuvant study evaluating ARV-471 or anastrozole in post-menopausal women with ER+/HER2– localized breast cancer. ARV-471 is an orally bioavailable PROteolysis TArgeting Chimera (PROTAC®) small molecule that induces active degradation of the ER via recruitment of the cereblon E3 ligase. Anastrozole is an aromatase inhibitor (AI) that is commonly used (and considered SOC) in the neoadjuvant treatment of post-menopausal women with HR+ breast cancer.

This trial will provide the first opportunity to evaluate the pharmacodynamic effects, safety, and activity of ARV-471 in a treatment-naïve setting. It will also allow evaluation of the PD activity (mainly via Ki-67) of ARV-471 or anastrozole in the treatment-naïve setting. These results will help inform future definitive studies in early and late-stage ER+/HER2– breast cancer.

Overall Design:
This is a Phase 2, open-label, randomized, non-comparative proof of concept study of ARV-471 or anastrozole in participants with ER+/HER2– breast cancer amenable to definitive surgical resection. The main goal of this study is to evaluate the biological activity of ARV-471 and anastrozole, respectively.

Participants will be randomized in a 2:1 manner to receive treatment on one of two treatment arms for approximately 5.5 months:

- Arm A: ARV-471 200 mg PO, daily and continuously until the day before surgical resection (no later than C6D18 + 14 days)
- Arm B: anastrozole 1 mg PO, daily and continuously until the day before surgical resection (no later than C6D18 + 14 days)

Stratification will occur based on the following features of the participant's breast cancer:

- Size of primary breast tumor (T-stage): ≤2 cm, >2 to <5 cm, or ≥5 cm.
- Ki-67 score (assessed locally): <20% or ≥20%

Participants will have a screening biopsy, an on-treatment biopsy on C1D15 (+5 days), and surgical resection approximately 5.5 months after starting treatment (C6D18 ± 14 days). Participants will return for follow up 30 days (+7 days) after definitive surgical resection. After surgery, participants will receive standard of care radiation and systemic therapy (chemotherapy, endocrine therapy, etc.) in accordance with local practice guidelines per the treating physician's discretion. No participant should take study drug dispensed for the

trial after surgical resection, and no study drug should be dispensed after surgical resection.

A Safety Review Committee will review all data from participants enrolled in this study.

Number of Participants (Planned):
Approximately 150 participants are expected to be enrolled (~100 participants in Arm A and 50 participants in Arm B). It is estimated that this sample size will provide approximately 120 (80 in Arm A and 40 in Arm B) participants with evaluable paired biopsies (screening and C1D15 biopsies).

Diagnosis and Main Criteria for Eligibility:
Participants must meet all of the inclusion and exclusion criteria specified in Section 5 of the protocol.

Participants for whom neoadjuvant endocrine monotherapy is deemed appropriate are eligible for inclusion in this study only if all the following key inclusion criteria are met:

Type of participant and target disease characteristics:

- Post-menopausal females ≥18 years
  - Post-menopausal status will be defined by at least one of the following: prior bilateral oophorectomy, age ≥60, or age <60 and amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, ovarian suppression, or any additional medical intervention that may have induced amenorrhea) and follicle stimulating hormone/estradiol in the postmenopausal range
- Histologically or cytologically confirmed ER+ and HER2– breast cancer (per local assessment). ER and HER2 status must be documented:
  - ER+ disease, with ER staining of ≥10% of tumor cell nuclei by IHC per ASCO/CAP Guidelines (Allison 2020).
  - HER2– disease by either IHC or in situ hybridization per ASCO/CAP guidelines
  - Ki-67 score ≥5%, analyzed locally
- Clinical T1c-T4c, N0-N2, M0 breast cancer amenable to definitive surgical resection, without bilateral breast ductal carcinoma in situ or invasive breast cancer
- The primary tumor must be at least 1.5 cm by imaging
- ECOG performance status of 0 or 1
- Willingness to undergo a screening biopsy, an on-treatment biopsy and surgical resection

Laboratory Findings:

- Adequate bone marrow function defined as follows (with no transfusion of blood products or use of hematopoietic growth factors in the 28 days prior to enrollment):
- Absolute neutrophil count of ≥1500/mm^3 or ≥1.5 × 10^9/L

- Platelets of ≥100,000/mm^3 or ≥100 ×10^9/L
- Hemoglobin ≥9 g/dL
- aPTT ≤1.25 × 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.
- Adequate renal function defined as serum creatinine of ≤1.5 × ULN or an estimated creatinine clearance of ≥60 mL/min by Cockcroft Gault
- Adequate liver function defined as:
- Total serum bilirubin of ≤1.5 × ULN unless the participant has documented Gilbert syndrome. Participants with Gilbert syndrome must have total serum bilirubin ≤3 × ULN.
- AST and ALT of ≤2.5 × ULN

Participants will not be eligible for this study if any of the following key exclusion criteria are met:
Medical conditions:

- Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or cervical carcinoma in situ
- 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
  - Symptomatic pulmonary embolism or other clinically significant episode of thromboembolism
- Any of the following in the previous 6 months:
  - Congenital long QT syndrome
  - Torsade de Pointes
  - Sustained ventricular tachyarrhythmia and ventricular fibrillation
  - Left anterior hemiblock (bifascicular block)
  - Ongoing cardiac dysrhythmias of NCI CTCAE ≥Grade 2
  - Atrial fibrillation of any grade (≥Grade 2 in the case of asymptomatic lone atrial fibrillation)
- QTcF >470 msec
- Active, uncontrolled bacterial, fungal or viral infection, including HBV, HCV, and HIV or AIDS-related illness

- Active inflammatory gastrointestinal disease, chronic diarrhea, known uncontrolled diverticular disease, or previous gastric resection or lap band surgery
- Cirrhosis meeting criteria for Child Pugh B and C

Prior/concomitant therapy:

- Prior treatment for breast cancer including systemic therapy (eg, chemotherapy, hormonal therapy), radiation, surgery, or any investigational agents
- Any live vaccines within 14 days of planned start of first dose of study drug.
- Taking the following agents within 14 days of C1D1 unless otherwise specified:
  - Sensitive P-gp substrates or P-gp substrates with narrow therapeutic indices
  - Strong CYP3A4 inhibitors or inducers
  - Any medications with known QT risk, and/or are associated with a risk of Torsades de Pointes, within 7 days of C1D1
- Major surgery (as defined by the Investigator) within four weeks of first dose of study drug

Allergy and other drug reactions:

- History of allergy or reaction to any of the drug components for ARV-471 or anastrozole, including patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Other criteria:

- Inability to take oral medication without crushing, dissolving, or chewing tablets

Study Intervention, Dosage and Mode of Administration:
ARV-471 will be dosed at 200 mg administered orally once a day, continuously throughout each 28-day cycle until the day before surgery (no later than C6D18 + 14 days).

Anastrozole will be dosed at 1 mg administered orally once a day, continuously throughout each 28-day cycle until the day before surgery (no later than C6D18 + 14 days).

Duration of Treatment:
Planned Study Duration: Approximately 18 months (time from first participant enrolled until all participants have completed the study).
Planned Treatment Duration: Participants will continue treatment with ARV-471 or anastrozole for approximately 5.5 months prior to undergoing surgical resection (no later than C6D18 + 14 days), and in the absence of disease progression that may jeopardize the opportunity for definitive surgery, unacceptable toxicity, participant withdrawal or Investigator's decision or other criteria as defined in Section 7 of the protocol.

Statistical Methods:
Sample Size Determination
This is a Phase 2 proof of concept study designed to generate data informing future studies about ARV-471. There are no plans for formal comparisons between ARV-471 and anastrozole. Descriptive statistics (including point estimates and two-sided confidence intervals) will be provided for all parameters of interest. Approximately 150 participants will be randomized to the two treatment arms in a 2:1 ratio (100 participants to the ARV-471 arm and 50 participants to the anastrozole arm). These numbers were chosen to provide meaningful information about the primary endpoint, ie, changes (on-treatment

C1D15 vs baseline) in Ki-67 expression levels after approximately 2 weeks of treatment with ARV-471 or anastrozole. Assume that 80% of the randomized participants will provide valid Ki-67 measurements from both their baseline and C1D15 biopsies. Also assume that Ki-67 will reduce to approximately 20 to 40% of their corresponding baseline values after 2 weeks of treatment. The width of the 80% CIs of the mean percentage Ki-67 with ARV-471 will not exceed 14% and the width of the 95% CIs will not exceed 21.6%. The planned sample size will provide estimates for the treatment effect in terms of the reduction of Ki-67 with reasonable precision.

Primary Safety/Efficacy Analyses
Statistical analyses for the primary and secondary endpoints are summarized here. Additional analyses are described in Section 9 and in the SAP.

Analyses for PD endpoints including the primary endpoint:
Ki-67 expression will be assessed by immunohistochemical staining in a central laboratory.

Analysis of Ki-67 reduction will be based on a Ki-67 evaluable population. The log-transformed percentage change in Ki-67 after approximately 2 weeks of treatment, ie, the ratio between the Ki-67 measurements obtained from C1D15 visit and baseline, will be modelled using a GLM, with both stratification factors (ie, baseline Ki-67 score and the tumor size) and treatment as covariates. Treatment effects for each arm will be summarized using the LSM and their two-sided confidence intervals on the log scale. In addition, for easier interpretation of the data, the treatment effects will be back transformed and expressed as the geometric means and their confidence intervals on the original percentage scale by treatment arm. Similar modeling will be applied to ER data.

CCCA at week 2 is defined as Ki67 score $\leqslant$2.7%. An estimate of the difference in CCCA rates and corresponding 80% as well as 95% CIs will be calculated using Cochran Mantel-Haenszel methodology. Odds ratios between the treatment will be provided along with corresponding CIs.

Analyses for clinical and pathologic response endpoints:
pCR is defined as no invasive cancer in the breast and sampled axillary lymph nodes following completion of neoadjuvant systemic therapy.

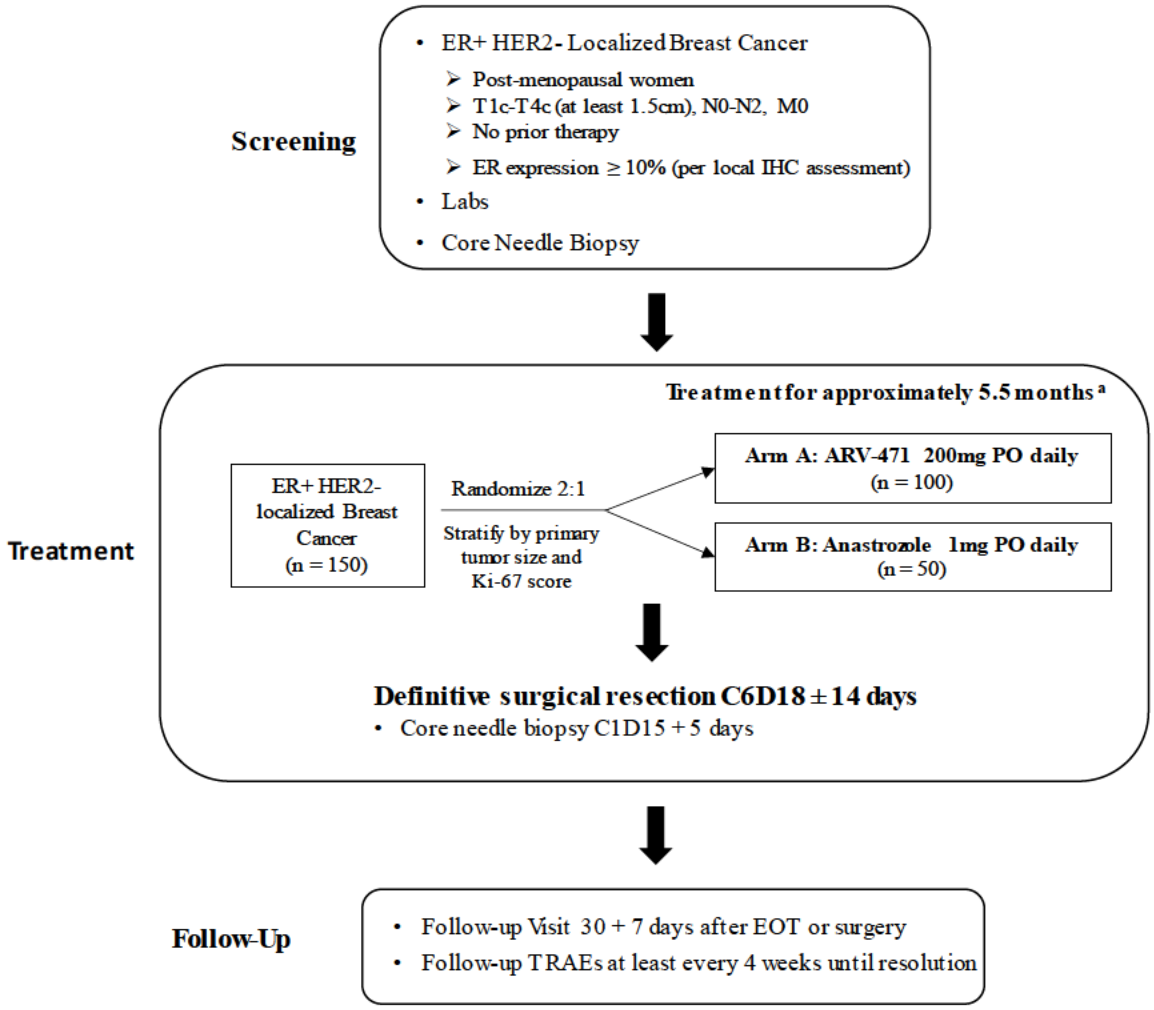
mPEPI score is derived from factors assigned a numerical score following neoadjuvant endocrine therapy, including Ki67 expression in the surgical specimen, pathologic tumor size and lymph node status. The proportion of participants achieving mPEPI score 0 after treatment will be evaluated.

To support the secondary objective of evaluating clinical and pathologic response, binary or categorical endpoint such as pathologic stage, pCR, and participants with mPEPI score 0 at the time of surgical resection (C6D18 ± 14 days), rates of breast conserving surgery, radiographic response per mRECIST in the primary tumor during cycle 6 will be summarized and estimated rate will be computed by treatment arm along with the exact CI using Wilson method; for caliper-based response on C6D1, best percentage change from

baseline will be graphed by treatment arm. All clinical and pathologic response will be listed for randomized participants by treatment arm.

Safety analysis will be performed for all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE v5.0. All TEAEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade per NCI CTCAE v5.0 criteria. The extent of exposure including number of doses, duration of treatment, and dose modifications will be summarized by treatment arm. A summary of deaths with reasons will be provided for all treated participants.

1.2. Schema



IHC=immunohistochemistry; PO=oral; TRAE=treatment-related adverse event.

a. ARV-471 or anastrozole should be taken daily and continuously until the day before surgical resection.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to Section 8 for information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA (Table 1, Table 2, and Table 3), in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1 Screening Activities

Procedure[a]	Notes *All items to be performed within 28 days of C1D1 unless otherwise noted*
Informed consent	Obtain prior to performing testing for eligibility. Register in IRT system to obtain Participant Study ID.
Inclusion/exclusion criteria	See Section 5.1 and Section 5.2
Medical history	Include disease process (eg, staging) and concurrent illness, including prior treatments.
Full physical examination	Caliper-based measurement of the primary breast tumor is required.
Vital signs	Includes height, weight, temperature, BP, heart rate, respiratory rate (record in sitting or semi-recumbent position after five minutes rest).
ECOG PS	ECOG should be 0 or 1 during screening. See Appendix 10.
ECG	Screening ECG will be a single 12-lead ECG, performed on site or vendor machines.
Review of concomitant medications	All medications or medical treatments including over-the-counter medications and/or herbal supplements taken up to 28 days prior to enrollment.
AE/SAE monitoring	Reporting starts at the time the participant provides informed consent. See Section 8.3.
Hematology	Complete blood count with differential. See Appendix 2.
Chemistry	See Appendix 2.
Coagulation	See Appendix 2.
Urinalysis	Urine dipstick testing is acceptable. See Appendix 2.
Viral disease screening	See Appendix 2[a] HIV testing if required by local regulations. See COVID information in Appendix 9.
Documentation of clinical TNM stage	Clinical TNM stage, along with the imaging modality utilized for staging, must be documented in the eCRF. The size of the primary tumor (T-stage) by imaging will be used to stratify participants (see Section 8.1.1).
Tumor Biopsy	Core needle biopsies of the primary breast tumor must be collected during screening. Fine needle aspirations are not allowed. See Section 8.6.1 and the Laboratory Manual for details.
Imaging	Imaging of the breast is required using ultrasound, MRI with contrast and/or mammogram. If imaging already has been performed as part of SOC, and will be within 4 weeks prior to C1D1, repeat imaging will not be required during screening. Full staging scans during or prior to screening may be performed, if necessary, at the discretion of the investigator as per SOC.

a. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Table 2 Schedule of On-Treatment Activities

Visit Identifier Abbreviations used in this table may be found in Appendix 12	Treatment Period (28-day cycles)					Follow Up	Notes
Cycle	1		2, 3, 4, 5	6			
Treatment Day	1[a]	15 (biopsy)	1	1	18[b] (surgery)	30 Days After Surgery	
Visit Window (days)	N/A	+5	±2	±2	±14	+7	
Physical Examination							See Section 8.2 for additional information. Physical examinations to be completed before administration of study intervention.
Full physical examination	X						All physical exams must include a caliper-based measurement of the primary breast tumor. Abbreviated physical exam is symptom based. See Section 8.2.1.
Abbreviated physical exam		X[c]	X	X	X	X	
Weight	X		X	X			
Vital signs	X	X	X	X	X	X	Temperature, BP, heart rate, respiratory rate (record in sitting or semi-recumbent position after 5 minutes rest). On clinic days perform pre-dose. See Section 8.2.2.
Pre-dose ECG (standard 12-lead)	X	X[c]	X*	X			Triplicate 12-lead ECGs performed on vendor machines. See Section 8.2.3. *For C2D1 an additional 4h post-dose ECG is required.
Performance Status							
ECOG Performance status	X						See Appendix 10
Randomization and Study Intervention and Other Treatments							
Randomization	X (C1D1, up to -3 days)						Randomization must occur after having carefully reviewed all eligibility criteria and confirmed they are satisfied. At randomization, participant number and treatment arm are assigned.
ARV-471 administration *(Arm A)*	Daily and continuously until the day before surgical resection (no later than C6D18 + 14 days)						By mouth daily. See Section 6 for additional information

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Treatment Period (28-day cycles)**					**Follow Up**	**Notes**
Cycle	**1**		**2, 3, 4, 5**	**6**			
Treatment Day	**1[a]**	**15 (biopsy)**	**1**	**1**	**18[b] (surgery)**	**30 Days After Surgery**	
Visit Window (days)	**N/A**	**+5**	**±2**	**±2**	**±14**	**+7**	
Anastrozole administration ***(Arm B)***	Daily and continuously until the day before surgical resection (no later than C6D18 + 14 days)						By mouth daily. See Section 6 and label for additional information.
Compliance/ patient diary ***(Arm A/B)***	X	X	X	X	X		Confirm and reconcile return of the bottle and remaining tablets of ARV-471 and anastrozole, as well as the completed patient diary (see Section 6.4)
Concomitant treatment(s)	Throughout						See Section 6.8
Efficacy Assessments							See Section 8.1
Tumor biopsy		X					Core biopsies during C1 must be obtained from the same site as the screening biopsy, if possible. Specimens must be processed and shipped per the Laboratory Manual. See Section 8.6.1.
Surgical resection					X[c]		See Section 6.9.
Imaging			X*		X**		The same imaging modality used for screening (breast ultrasound, breast MRI with contrast, and/or mammogram) should be used throughout. See Section 8.1.1. * On C4D1 (±7 days) only. ** Must be performed within 7 days prior to surgical resection.
Safety Assessments							See Section 8.2 and 8.3.
Serious and nonserious AE monitoring	Throughout						See Section 8.3 and Appendix 3. Participants continuing to experience treatment-related toxicity will continue to be followed at least every four weeks until resolution or determination (in the clinical judgment of the Investigator) that no further improvement in the toxicity is expected.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Treatment Period (28-day cycles)**					**Follow Up**	**Notes**
Cycle	**1**		**2, 3, 4, 5**	**6**			
Treatment Day	**1[a]**	**15 (biopsy)**	**1**	**1**	**18[b] (surgery)**	**30 Days After Surgery**	
Visit Window (days)	**N/A**	**+5**	**±2**	**±2**	**±14**	**+7**	
Laboratory Assessments							See Section 8.2.4 and Appendix 2
Hematology	X		X	X	X		
Blood chemistry	X		X	X	X		
Coagulation	X				X		
Urinalysis	X						

Note: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where participants are in the clinic, they will be instructed to hold their dose, which will be administered by study staff onsite.

a. If the screening physical exam, ECG, and labs are performed within 96 hours of C1D1, these tests do not need to be repeated on C1D1. However, if screening ECG is obtained on site machine, then it needs to be repeated on vendor machine on C1D1. If screening ECG is being used for C1D1, it must be done in triplicate.
b. Physical exam and safety labs may be performed within 72 hours prior to surgery.
c. May be performed up to 72 hours before biopsy

Table 3 PK Sampling Schedule for Participants Receiving ARV-471

Visit Identifier	CYCLE 1	CYCLE 2	CYCLE 6
	Day 15 (biopsy)	Day 1	On day of surgery Day 18
Visit Window	(+5 days)[a]	(±2 days)	(±14 days)[b]
Pre-dose		X	
1 hour (±15 min) post-dose		X	
2 hours (±15 min) post-dose		X	
4 hours (±30 min) post-dose		X	
Pre-biopsy	X		
Pre-surgery			X

a. May be collected up to 72 hours before biopsy
b. May be collected up to 72 hours before surgery

Note: On days of scheduled clinic visits for PK, participants should be instructed not to take their study drug treatment at home, as it will be administered in clinic on those days (Section 6.1.1.1 and 8.4). ARV-471 should be taken on the day of biopsy and the day the pre-surgical study labs are collected. **The date and time of the two most recent ARV-471 doses (day prior to PK sampling and day of PK sampling), and the date and time of the PK collection must be documented.**

2. INTRODUCTION

2.1. Study Rationale

This is a Phase 2 neoadjuvant, non-comparative, POC study, evaluating ARV-471 or anastrozole in post-menopausal women with ER+/HER2– localized breast cancer.

Clinical trials evaluating pre-operative endocrine therapy in ER+/HER2– breast cancer allow for rapid assessment of novel therapeutic approaches (Guerrero-Zotano 2017; Denduluri 2018). Pre-operative therapy can potentially downstage and improve suitability of breast conservation. Endocrine therapy is the therapeutic mainstay for ER+ breast cancer and targets ER activity and/or estrogen synthesis; however, many patients experience disease relapse or treatment resistance. Up to 20% of patients diagnosed with early-stage breast cancer relapse in the first 10 years, often with distant metastases (Johnston 2020).

Several trials evaluating pre-operative endocrine therapy have focused on biologic activity endpoints in tumor samples (Ellis 2008; Smith 2005; Ellis 2011). Ki-67 has been used as biomarker to assess the activity of agents targeting the ER pathway. Several large trials demonstrate results in the neoadjuvant setting correlate to relapse free survival after definitive surgical resection (Smith 2020, Ellis 2008) and outcomes in the adjuvant or metastatic setting (Guerrero-Zotano 2017). For example, the improved Ki-67 suppression with AIs compared with tamoxifen in the neoadjuvant setting in the IMPACT and P024 trial (Ellis 2008, Smith 2005) parallels the improved disease-free survival seen with AIs in the adjuvant setting (The BIG 1-98 Collaborative Group 2005, Howell 2005). Furthermore, the similarity in Ki-67 suppression between nsAIs and sAIs in the neoadjuvant setting (Ellis 2011) parallels the similar disease-free survival with these agents in the adjuvant setting (Goss 2013, Smith 2017).

ARV-471 is an orally bioavailable PROteolysis TArgeting Chimera (PROTAC®) small molecule that induces active degradation of the ER via recruitment of the cereblon E3 ligase. In the ongoing FIH study, ARV-471 has demonstrated a tolerable safety profile, robust ER degradation, and preliminary evidence of clinical activity in participants with advanced/metastatic breast cancer who received prior CDK 4/6 inhibitors (Section 2.2.1.1.5; Hamilton 2022). Based on these data in combination with pre-surgical trials demonstrating SERDs have biological activity and a tolerable safety profile in early breast cancer (Lerebours 2016, Kuter 2012, Ma 2020, Hurvitz 2022a), ARV-471 is expected to be tolerable and lead to clinical responses in the neoadjuvant setting.

This trial will provide the first opportunity to evaluate the biologic activity, clinical activity, and safety of ARV-471 in a treatment-naïve setting.

Anastrozole is an AI that is commonly used in the neoadjuvant treatment of post-menopausal women with HR+ HER2– breast cancer both in clinical practice and in clinical trials (Ma 2020, Hurvitz 2020, Hurvitz 2022a). Anastrozole has also been approved for the treatment of HR+ breast cancer in the adjuvant and advanced/metastatic setting, and these results will help inform future definitive studies of ARV-471 in early- and late-stage ER+/HER2– breast cancer.

2.2. Background

In 2020, there were 2.3 million women diagnosed with breast cancer and 685,000 deaths globally (Sung 2021). According to the World Health Organization, as of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. HR+, defined as expression of ER and/or PgR, is the most common subtype encompassing approximately 80% of all breast cancers (Li 2020).

Surgery is the cornerstone of treatment for early and locally advanced breast cancer and is often combined with radiation therapy and/or systemic anti-cancer therapy. In HR+ HER2– breast cancer, neoadjuvant chemotherapy is used as part of SOC to increase surgical options (eg, breast conservation) in patients with large tumors or lymph node involvement. Although the role of NET in this population is less clear, it may be used as part of SOC. NET provides a significantly less toxic alternative to chemotherapy that can lead to clinical responses in up to approximately 70% of patients (Ellis 2011). A meta-analysis comparing NET and neoadjuvant chemotherapy demonstrated no significant differences in the rates of clinical response and breast conservation (Spring 2016).

In post-menopausal women with HR+ HER2– breast cancer, AIs have shown to have superior efficacy compared with tamoxifen. In the P024 neoadjuvant trial of postmenopausal women with HR+ invasive breast cancer not eligible for BCS, clinical ORR was 55% for women receiving letrozole vs 36% for those receiving tamoxifen ($p<0.001$) (Ellis 2008). The proportion of women able to undergo BCS at approximately 4 months was 45% in the letrozole group and 35% in the tamoxifen group ($p=0.022$) (Ellis 2008). In the PROACT trial of postmenopausal women with operable or potentially operable locally advanced HR+ breast cancer, clinical ORR was 49.7% for women who received anastrozole only and 39.7% for those who received tamoxifen only (odds ratio 1.50 [95% CI 0.96-2.34], $p=0.08$) (Cataliotti 2006). Forty three percent of women on anastrozole had improvement in feasible surgery at baseline to actual surgery as compared to 30.8% for tamoxifen (odds ratio 1.69 [95% CI 1.01–2.81], $p=0.04$) (Cataliotti 2006). In the IMPACT trial of postmenopausal women with operable or potentially operable locally advanced ER+ breast cancer, the clinical ORR was 37% for women treated with anastrozole only, 36% for tamoxifen, and 39% for anastrozole and tamoxifen (Smith 2005). The odds ratio for ORR for anastrozole vs tamoxifen was 1.05 (95% CI 0.61-1.81, $p=0.87$) (Smith 2005). However, in women requiring mastectomy at baseline, 46% of women treated with anastrozole were deemed by a surgeon to be eligible for BCS as compared to 22% with tamoxifen (odds ratio 2.94; 95% CI 1.11-7.81; $p=0.03$) (Smith 2005). Furthermore, a pooled analysis of 6 neoadjuvant trials of the 3rd generation AIs (anastrozole, letrozole, and vorozole) showed significant benefit of AIs over tamoxifen in clinical response rate (odds ratio 1.69, 95% CI 1.36-2.10; $p<0.001$), and radiographic response (odds ratio 1.49; 95% CI 1.18-1.89; $p<0.001$) (Spring 2016). In a pooled analysis of 4 trials of anastrozole and letrozole, AIs showed significant benefit over tamoxifen in radiographic response and BCS (odds ratio 1.62; 95% CI 1.24-2.12; $p<0.001$) (Spring 2016).

Several trials have evaluated whether SERDs offer additional benefit compared to AIs in early breast cancer. Data generated on fulvestrant suggest similar Ki-67 reduction, clinical

response, and safety profile compared to AIs in in the pre-surgical setting (Lerebours 2016; Ma 2020; Quenel-Tueux 2015; Robertson 2013). Two novel oral SERDs have been evaluated in the pre-surgical setting: AZD9496 and giredestrant. In a WOO study, AZD-9496 (no longer in clinical development) was tolerable but did not show improved Ki-67 reduction compared to fulvestrant, which may be attributable to suboptimal exposure (Robertson 2020). Giredestrant showed a tolerable safety profile and improved Ki-67 reduction compared to anastrozole (reduction from baseline to Week 2 geometric mean=80%, 95% CI: −85% - −72% vs 67%, 95% CI: −75 - −56%; p=0.0222) (Hurvitz 2022a).

2.2.1. Clinical Overview

2.2.1.1. ARV-471

ARV-471 is a potent, selective, orally bioavailable PROteolysis TArgeting Chimera (PROTAC®) small molecule that induces active degradation of the ER. ARV-471 is being developed for the treatment of patients with ER+/HER2– locally advanced or metastatic breast cancer. ARV-471 works by recruiting an E3 ligase to ubiquitinate ER; once ubiquitinated, ER is degraded into small peptides by the proteasome.

The importance of ER degradation in HR+ metastatic breast cancer was established by the ER-targeted agent, fulvestrant. Fulvestrant has low oral bioavailability and is administered by intramuscular injection. In clinical trials, fulvestrant results in 40-60% degradation of ERs (Robertson 2013, Robertson 2001, Kuter 2012).

ARV-471 is orally administered, and in nonclinical studies demonstrated potent (<1 nM) and robust (>90%) ER degradation, even in the presence of clinically relevant ER mutations (Y537S and D538G). ARV-471 may have potential advantages over fulvestrant and other orally available SERDs. While SERDs destabilize ER and indirectly lead to ER degradation, ARV-471 actively induces ER degradation, which may lead to less drug resistance. Furthermore, ARV-471 demonstrates superior tumor growth inhibition compared to fulvestrant in a Y537S ESR1 mutant patient-derived xenograft (ARV-471 IB).

2.2.1.1.1. Mechanism of Action

ARV-471 is a hetero-bifunctional PROTAC® molecule that simultaneously binds ER and the cereblon E3 ligase complex, enabling protein-protein interactions between ER and the ligase complex. As a result, ER becomes poly-ubiquitinated on accessible lysine residues and, subsequently, undergoes targeted degradation by the proteasome for elimination from cells. Several nonclinical studies have been conducted to confirm the mechanism of action for ARV-471 as described in the ARV-471 IB. A summary of the data is described below.

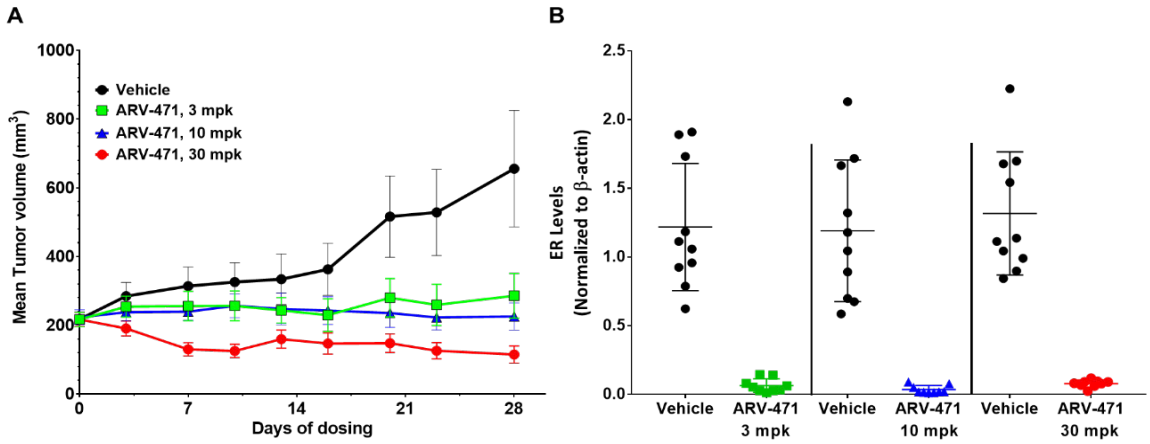
In vitro data demonstrated a dose-dependent decrease in ER levels in 6 ER+ cell lines (MCF7, T47D, BT474, CAMA-1, ZR751, and 134-VI). Furthermore, data from MCF7 cell lines provide evidence that ARV-471 degrades ERs via the proteasome by hijacking an intracellular E3 ligase. In MCF7 cells treated with ARV-471, a half-maximal DC_{50} of 0.9 nM was achieved with maximum ER degradation of >90%. When excess cereblon ligand (lenalidomide) or proteasome inhibitor (carfilzomib) was added, no ER degradation was seen. In vitro data also demonstrated that ARV-471 decreased levels of clinically relevant

mutant forms of ER, Y537S and D538G, in a dose-dependent manner, similar to fulvestrant. In a T47D cell line background, GI_{50} values were 50 nM for ER Y537S and 8 nM for ER D538G.

In addition to ARV-471, its epimer, ARV-473, was assessed for ER degradation activity (ARV471-00046-00-INVITRO). While both ARV-471 and fulvestrant reduced ER levels, ARV-473 did not reduce ER levels, even when tested at [redacted] µM. In an ER-dependent gene reporter assay (ARV471-00002-00-INVITRO), ARV-471 and ARV-473 had similar antagonist activity, indicating that ARV-471 has both antagonist and degradation activities against ER, whereas ARV-473 displays only antagonist activity.

In vivo data for MCF7 xenograft mouse models demonstrated both potent ER degradation and tumor growth inhibition after administration of ARV-471 by oral gavage for 28 days (Figure 1). At study termination, all doses of ARV-471 (3 mg/kg, 10 mg/kg, and 30 mg/kg daily) significantly reduced ER levels by >94% compared to placebo. Dose-dependent TGI was also observed: 85% at 3 mg/kg/day, 98% at 10 mg/kg/day, and 125% at 30 mg/kg/day.

Figure 1 ARV-471 Significantly Inhibits Tumor Growth and Reduces ER Levels in the MCF7 Xenograft Model



(A) Dose-dependent inhibition of tumor growth by ARV-471 in an orthotopic MCF7 mouse xenograft model. Female NOD/SCID mice were implanted with MCF7 cells in the mammary fat pad and ARV-471 administration (QD×28; PO) was initiated once the tumors reached 200 mm^3. Tumor volumes were evaluated twice per week for 28 days. ARV-471 at 3, 10, or 30 mg/kg inhibited growth of estradiol-stimulated MCF7 xenografts (85%, 98%, and 124% TGI, respectively). (B) At study termination, MCF7 xenografts were harvested and the ER levels in the xenografts were measured by immunoblotting and normalized to β-actin levels. At all dose levels of ARV-471, >94% loss of ER was seen by immunoblot.

Lastly, as described in Section 2.2.1.1.5, preliminary data from the FIH clinical trial ARV-471-mBC-101, demonstrates robust ER degradation in participants with wild type and mutant forms of ER.

2.2.1.1.2. Impact of Cereblon Substrates

Since ARV-471 engages the E3 ligase cereblon at the same binding site as IMiDs such as thalidomide, lenalidomide, and pomalidomide, ARV-471 was evaluated for its degradation effect on known cereblon neo-morphic substrates. In one study, overnight incubation of Ramos cells with increasing concentrations of ARV-471 did not lead to degradation of Ikaros, Aiolos, CK1α, and GSPT1, whereas the control IMiDs with known neomorphic substrate degradation activity (lenalidomide and CC-885) decreased levels of these neo-substrates. In another study with a cell line that expresses Sall4, a recently identified cereblon neomorphic substrate (Donovan 2018), partial degradation of Sall4 was seen with ARV-471, whereas complete degradation of Sall4 was seen with the IMiD lenalidomide at the same concentration (1 μM). No evidence of ARV-471-mediated Sall4 degradation was observed in a different cell line. While the teratogenic effects of the thalidomide class have been linked to their Sall4-degradation activity, no significant adverse effects due to potential partial loss of Sall4 are expected in the patient population included in this trial since most adult tissues do not express Sall4 (Tatetsu 2016).

2.2.1.1.3. Nonclinical Pharmacokinetics and Drug-Drug Interactions

Nonclinical PK data are provided in the ARV-471 IB. A summary of the key data is presented below.

The PK profile of ARV-471 in 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 volume of distribution at steady state), short to moderate $t_{1/2}$ (2.1 to 8.2 hr), and moderate to good oral bioavailability (27 to 65%).

Dose-dependent increases in ARV-471 exposure were 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 mg/kg), and monkey (1 and 3 mg/kg). [redacted]

Absorption:

Combined in vitro data suggests that ARV-471 is unlikely to be a substrate of intestinal efflux transporters including P-gp and BCRP. A moderate to good extent of oral absorption was generally obtained when ARV-471 was dosed as a solution formulation in nonclinical species, despite its low solubility and apparently low permeability in these in vitro assays (ARV-471 IB).

Preliminary DDI results from Study ARV-471-CPhm-103 indicated administration of PPI, esomeprazole, with ARV-471 did not affect the PK of ARV-471 when given with a moderate fat, moderate calories meal.

Metabolism and Drug-Drug Interactions:

[redacted]

Impact of CYP inhibitors/inducers or drug transporters on ARV-471

Study ARV-471-00063-00-INVITRO, a CYP reaction phenotyping study, was conducted consistent with current FDA guidance (FDA Guidance 2020). This study indicated CYP3A4 as the principal isoform responsible for CYP metabolism of ARV-471 (accounting for 85%). 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.

Available in vitro data suggest that ARV-471 is unlikely to be a substrate of P-gp, BCRP, OATP1B1, and OATP1B3.

Impact of ARV-471 on CYP, BCRP, and P-gp substrates

In vitro, ARV-471 (PF-07850327) is a reversible inhibitor of CYP2B6 with an IC_{50} of 16.0 µM. Initial DDI risk assessment based on the FDA Guidance for Industry (FDA 2020) indicated the potential for ARV-471 to inhibit CYP2B6 at clinically relevant concentrations associated with the 500 mg QD dose. 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. Consequently, patients enrolled in clinical trials will be allowed to receive sensitive CYP2B6 substrates or CYP2B6 substrates with narrow therapeutic indices. [redacted]

ARV-471 does not induce CYP1A2, 2B6, and 3A4 in vitro.

Nonclinical data indicate the potential of ARV-471 to inhibit human BCRP. However, based on preliminary PK and clinical data (n=8 participants receiving rosuvastatin concomitantly with ARV-471 as described in the ARV-471 IB), participants enrolled in this study will be allowed to receive sensitive BCRP substrates or BCRP substrates with narrow therapeutic indices.

Nonclinical data indicate the potential of ARV-471 to inhibit P-gp. A summary of restrictions on concomitant medications is provided in Section 6.8.1.

Refer to the most current ARV-471 IB version for additional information on ARV-471 metabolism and potential DDIs.

2.2.1.1.4. Nonclinical Safety and Toxicology

Nonclinical toxicology data is provided in the ARV-471 IB. A few key points are summarized below.

Results of hERG assays for ARV-471 were negative. The hERG IC_{50} and therapeutically relevant human C_{max} values for ARV-471 (using 500 mg ARV-471 QD as a reference) are separated by at least 69-fold.

The 7- and 28-day oral toxicity studies in rats and dogs have shown ARV-471 to be well tolerated after QD dosing up to 100 mg/kg/day in rats and 90 mg/kg/day in dogs. Across the studies, there were no consistent findings or patterns of effects in hematology or clinical chemistry. As tested in dogs, ARV-471 did not elicit any changes in ECG evaluations after daily dosing at 90 mg/kg/day for 28 days. [redacted]

As expected, ARV-471 had effects on the reproductive systems of both female and male animals and showed recovery or evidence of reversibility following discontinuation of dosing. Findings in male and female animals were consistent with the pharmacological action of ARV-471 at the ER and have been observed in other agents that target the ER (eg, fulvestrant) (US FDA Fulvestrant 2002).

[redacted]

2.2.1.1.5. Clinical Trial Data: Study ARV-471-mBC-101

Study ARV-471-mBC-101 is an ongoing FIH Phase 1/2 open-label, dose-escalation, and cohort expansion clinical trial of ARV-471 given alone or in combination with palbociclib (IBRANCE®) in participants with ER+/HER2– locally advanced or metastatic breast cancer. Preliminary analyses completed on participants in the monotherapy dose escalation portion (Part A) of the FIH study suggest a tolerable safety profile, robust pharmacodynamic activity (ER degradation), and evidence of early clinical activity in participants who received prior CDK 4/6 inhibitor therapy.

A summary of the findings from the monotherapy dose escalation and expansion can be found in the most current ARV-471 IB version.

2.2.1.2. Anastrozole

In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme (Anastrozole USPI).

Anastrozole is a selective nsAI. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone (Anastrozole USPI).

In the US, anastrozole is currently indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer and first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer. It is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to anastrozole (Anastrozole USPI).

In the EU, anastrozole is indicated for treatment of hormone receptor-positive advanced breast cancer in postmenopausal women and adjuvant (add-on) treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women, including those who have received two to three years of adjuvant tamoxifen (Anastrozole European Medicines Agency Committee for Medicinal Products for Human Use SmPC).

The dose of anastrozole is 1 mg tablet taken once a day (Anastrozole USPI).

Anastrozole is contraindicated in pregnant and premenopausal women. It is also contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the excipients (Anastrozole USPI). Additionally in the EU, it is specifically contraindicated in women who are breast feeding (Anastrozole European Medicines Agency Committee for Medicinal Products for Human Use SmPC).

Serious adverse reactions with anastrozole occurring in less than 1 in 10,000 patients, are: 1) skin reactions such as lesions, ulcers, or blisters; 2) allergic reactions with swelling of the face, lips, tongue, and/or throat. This may cause difficulty in swallowing and/or breathing; and 3) changes in blood tests of the liver function, including inflammation of the liver with symptoms that may include a general feeling of not being well, with or without jaundice, liver pain or liver swelling (Anastrozole USPI).

Common adverse reactions (occurring with an incidence of >10%) in women taking anastrozole included: hot flashes, asthenia, arthritis, pain, arthralgia, pharyngitis, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, pain, headache, bone pain, peripheral edema, increased cough, dyspnea, pharyngitis, and lymphedema (Anastrozole USPI).

In the ATAC trial, the most common reported adverse reaction (>0.1%) leading to discontinuation of therapy for both treatment groups was hot flashes, although there were fewer patients who discontinued therapy as a result of hot flashes in the anastrozole group (Anastrozole USPI).

As anastrozole lowers circulating estrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. Women with osteoporosis or at risk of osteoporosis, should have their bone mineral density assessed as per investigator's best medical judgement and based on local practice guidelines. Treatment or prophylaxis for osteoporosis may be initiated as appropriate and carefully monitored as per investigator's judgement.

Additional or updated information on anastrozole can be found in the most recent local product label.

2.3. Benefit/Risk Assessment

The main goals of this neoadjuvant study are to assess the biologic effects and safety of ARV-471 and anastrozole, respectively, in participants with early localized breast cancer. The study will enroll post-menopausal women with treatment naïve, ER+/HER2– breast cancer, amenable to definitive surgical resection, and randomize them to pre-operative treatment with ARV-471 or anastrozole. To allow participants the opportunity for clinical response, treatment will continue for approximately 5.5 months prior to surgical resection.

NET has therapeutic potential for patients with ER+ breast cancer and is currently used as SOC in select patients, such as post-menopausal women, or those with ER+ tumors (Korde 2021; Gradishar 2021) to increase the likelihood of breast conservation. It provides a significantly less toxic alternative to chemotherapy that can lead to clinical responses that are comparable to neoadjuvant chemotherapy (Spring 2016; Wang 2020). Although tamoxifen and AIs are commonly used (Section 4.2.2), an optimal NET regimen has yet to be determined. In the neoadjuvant setting, selective ER downregulators and degraders and nsAIs demonstrate similar safety profiles, clinical response rates, breast conservation rates, and Ki-67 reduction (Lerebours 2016; Ma 2020; Quenel-Tueux 2015; Robertson 2013; Hurvitz 2020).

Preliminary data from the ongoing FIH study with ARV-471 has shown that ARV-471 has a tolerable safety profile, leads to robust ER degradation (including in participants with ESR1 mutations), and results in clinical benefit that exceeds that of fulvestrant in participants previously treated with CDK 4/6 inhibitors (Hamilton 2022; Hurvitz 2022b; ARV-471 IB). Therefore, ARV-471 is expected to be tolerable and lead to clinical responses in the neoadjuvant setting.

2.3.1. Risk Assessment

In the ongoing FIH study, ARV-471 monotherapy Part A 30 to 700mg daily and Part B 200 and 500 mg is well tolerated. No DLTs were observed and MTD was not reached. Most TRAEs were grade 1 or 2. The most common TRAEs observed in ≥10% of patients treated

with ARV-471 (monotherapy therapy Parts A and B) were fatigue, nausea, arthralgia, and hot flush. There were no dose dependent increases in treatment related AEs.

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

Participant safety will be monitored closely throughout study participation (Appendix 3). The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objective	Endpoints
Primary	
Evaluate the effects of ARV-471 and anastrozole, respectively, on Ki-67 expression in tumors after 2 weeks of treatment	Percent change in Ki-67 expression between baseline and C1D15 tumor biopsies Estimand: See Section 9.1.2.1.
Secondary	
Evaluate the safety and tolerability of ARV-471 and anastrozole, respectively	Incidence of all adverse events, serious adverse events, and adverse events leading to study drug discontinuation
Evaluate the clinical and pathological response of ARV-471 and anastrozole, respectively	Pathologic stage, pathologic complete response (pCR) rate, and modified Pre-operative Endocrine Prognostic Index (mPEPI) score at the time of surgical resection (C6D18 ± 14 days); rates of breast conserving therapy; radiographic response of the primary tumor based on imaging during cycle 6; caliper-based response on C6D1
Exploratory	
Evaluate the effects of ARV-471 and anastrozole, respectively, on CCCA after 2 weeks of treatment	CCCA (Ki67 ≤2.7%) rates at C1D15
Evaluate ER degradation of ARV-471	Percent change in ER protein levels between baseline and C1D15
Evaluate the effects of ARV-471 and anastrozole, respectively, on Ki-67, and ER degradation by ARV-471 in tumors at the time of surgical resection.	Changes in ER and Ki-67 expression between baseline and Cycle 6 surgical tumor samples; Rates of CCCA in the Cycle 6 surgical samples.
Explore additional biomarkers that may be associated with the effects of ARV-471 in tumor tissue	Additional biomarkers may include, but are not limited to, PgR expression, [redacted]
Correlate exposure of ARV-471 with ER reduction	Correlate population PK model-derived PK parameters (AUC, C_{min}, C_{max}) with ER reduction or other response parameters

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, open-label, randomized, non-comparative POC study of ARV-471 or anastrozole in participants with ER+/HER2– breast cancer amenable to definitive surgical resection. The main goal of this study is to evaluate the biological activity of ARV-471 and anastrozole, respectively.

Participants will be randomized in a 2:1 manner to receive treatment on one of two treatment arms for approximately 5.5 months:

- Arm A: ARV-471 200 mg orally, daily, and continuously until day before surgical resection (no later than C6D18 + 14 days)
- Arm B: anastrozole 1 mg orally, daily, and continuously until day before surgical resection (no later than C6D18 + 14 days)

Stratification will occur based on the following features of the participant's breast cancer:

- Size of primary breast tumor (T-stage): ≤2 cm, >2 to <5 cm, or ≥5 cm.
- Ki-67 score (assessed locally): <20% or ≥20%

Participants will have a screening biopsy, an on-treatment biopsy on C1D15 (+5 days), and surgical resection approximately 5.5 months after starting treatment (C6D18 ± 14 days). Participants will return for follow up 30 days (+7 days) after definitive surgical resection. After surgery, participants will receive SOC radiation and systemic therapy (chemotherapy, endocrine therapy, etc.) in accordance with local practice guidelines per the treating physician's discretion. No participant should take study drug dispensed for the trial after surgical resection, and no study drug should be dispensed after surgical resection.

Approximately 150 participants are expected to be enrolled (~100 participants in Arm A and 50 participants in Arm B). It is estimated that this sample size will provide approximately 120 (80 participants in Arm A and 40 participants in Arm B) participants with evaluable paired biopsies (screening and C1D15 biopsies) as described Section 8.6.1.

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for Selection of Patient Population

This trial will enroll post-menopausal women with newly diagnosed and treatment naive ER+/HER2– breast cancer that is amenable to definitive surgical resection. Patients with HER2 over–expressing tumors are excluded as these patients receive SOC treatments that include HER2-targeted agents. This population selected includes participants that are typically considered for NET. Participants must also have tumor that is at least 1.5 cm as confirmed by imaging due to biopsy requirements for this study.

4.2.2. Rationale for Selection of Control Arm

In ER+/HER2– breast cancer, an optimal endocrine-based neoadjuvant regimen has yet to be established. AIs have been shown to have superior clinical activity to tamoxifen in

post-menopausal women (Section 2.2). NsAIs (anastrozole, letrozole) and sAIs (exemestane) have similar safety profiles and have shown similar efficacy in the neoadjuvant setting. The Z1031 study compared anastrozole, letrozole, and exemestane as NET in post-menopausal women with Stage II-III HR+ breast cancer and found all treatments to be similar (Ellis 2011). The clinical response rates for anastrozole, letrozole, and exemestane were 69.1% (95% CI, 60.1% to 77.1%), 74.8% (95% CI, 66.3% to 82.1%), and 62.9% (95% CI, 53.8% to 71.4%), respectively (Ellis 2011). At surgery at approximately 16 weeks, the geometric change in Ki-67 was -78% (standard error of the mean 4%) for anastrozole, -81.2% (standard error of the mean 3.5%) for exemestane, and -87.1% (standard error of the mean 2.8%) for letrozole (Ellis 2011). There was no significant difference in Ki-67 suppression between treatment arms (Kruskal-Wallis p=0.45, adjusted for three-way comparison) (Ellis 2011).

Anastrozole has been used as a control arm for several recent neoadjuvant studies in breast cancer including the ALTERNATE, NeoMONARCH, and coopERA clinical trials. In randomized Phase 2 and 3 neoadjuvant trials, clinical objective response rates for patients receiving anastrozole monotherapy have ranged from 37% to 69.1% at surgery at 3 to 6 months (Smith 2005; Cataliotti 2006; Lerebours 2016; Quenel-Tueux 2015; Ellis 2011). In these trials, the rates of BCS for patients receiving anastrozole ranged from 43% to 57.8% (Smith 2005; Cataliotti 2006; Lerebours 2016; Ellis 2011). Anastrozole has also been used in trials assessing Ki-67 including the Z1031, IMPACT, NeoMONARCH, and coopERA clinical trials. In these 4 trials of postmenopausal women with early or locally advanced HR+ breast cancer, Ki-67 reduction (geometric mean change) at 2 weeks ranged from -63% (90% CI, −73 to −49) to -76% (95% CI -81.9 to -68.2) for patients receiving anastrozole (Dowsett 2005; Smith 2005; Ellis 2011; Hurvitz 2020; Hurvitz 2022a). Given the clinical activity of anastrozole in the neoadjuvant setting and thus common usage as a SOC and control arm, it was chosen as the control arm for this study.

4.2.3. Rationale for Duration of Treatment

All participants will be treated with NET for approximately 5.5 months prior to definitive surgical resection. It takes a few months to achieve clinical responses or tumor shrinkage from NET, however the optimum duration of NET remains unclear. Four to six month treatment windows have been used by several NET trials in ER+/HER2– breast cancer (Guerrero-Zotano 2017; Barchiesi 2020; Martí 2021).

4.2.4. Collection of Retained Research Samples

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

4.3. Justification for Dose

4.3.1. ARV-471

In the FIH monotherapy dose escalation study, ARV-471-mBC-101, no DLTs were observed, and an MTD was not reached. The MAD was 700 mg (administered at 400 mg in the morning and 300 mg in the evening in 3 of the 4 participants to lessen pill burden). Two RP2Ds, 200 mg daily and 500 mg daily, were selected for Phase 2 evaluation in the ongoing

monotherapy expansion of ARV-471-mBC-101 to support dose selection for Phase 3 evaluation of ARV-471 in metastatic breast cancer. Both doses resulted in steady state C_{max} and AUC_{24} values that significantly exceeded thresholds associated with tumor regression in nonclinical models, eg, MCF7-tumor bearing NOD/SCID mice treated at 30 mg/kg. Both doses are also below the NOAEL of 100 mg/kg/day in female rats (the most sensitive species in nonclinical toxicology studies), which is equivalent to a human dose of approximately 960 mg daily. Additionally, both doses had an acceptable safety profile, and ER degradation was demonstrated in participants across all doses in which paired biopsies were obtained.

In Part B monotherapy expansion, no meaningful differences were noted between the 200 mg and 500 mg dose levels in overall safety, such as TRAEs, TEAEs leading to discontinuations, or dose interruptions (Hurvitz 2022b). Clinical benefit (as measured by CBR) was seen at both doses with no clear differences observed between the 200mg and 500mg dose levels. No significant dose-response relationship was seen between the 200 mg and 500 mg daily doses in a heavily pretreated population.

Considering the benefits and risks in this early stage curable population, a 200-mg dose of ARV-471 was selected for this study based on the totality of safety, PK, PD, and efficacy data available from Part A dose escalation and backfill and Part B expansion of the FIH study as of 06 June 2022 (Hurvitz 2022b; ARV-471 IB).

4.3.2. Anastrozole

The approved dose and schedule of anastrozole will be used per the USPI (or local label).

4.4. Safety Review Committee

The SRC will review all data from participants enrolled in this study. The SRC will be responsible for making recommendations as to whether it is scientifically and ethically appropriate to continue enrollment, discontinue treatment groups, or stop the study.

The SRC membership, will be comprised of selected study principal investigators and Sponsor representative(s). The SRC is responsible for reviewing and evaluating data at least every three months.

4.5. Start and End of Study Definition

The start of the trial is defined as the first participant's first visit. End of study is defined as the last participant's last study visit or follow-up phone call. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

Participants for whom neoadjuvant endocrine monotherapy is deemed appropriate are eligible to be included in the study only if **all** of the following criteria apply:

Age and Sex:

1. Post-menopausal females ≥18 years
    - Post-menopausal status will be defined by at least one of the following: prior bilateral oophorectomy, age ≥60, or age <60 and amenorrheic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, ovarian suppression, or any additional medical intervention that may have induced amenorrhea) and FSH/estradiol in the postmenopausal range

Type of Participant and Disease Characteristics:

2. Histologically or cytologically confirmed ER+ and HER2– breast cancer (per local assessment). ER and HER2 status must be documented:
    - ER+ disease, with ER staining of ≥10% of tumor cell nuclei by IHC per ASCO/CAP Guidelines (Allison 2020).
    - HER2– disease by either IHC or in situ hybridization per ASCO/CAP guidelines
    - Ki 67 score ≥5%, analyzed locally
3. Clinical T1c-T4c, N0-N2, M0 breast cancer amenable to definitive surgical resection, without bilateral breast ductal carcinoma in situ or invasive breast cancer
4. The primary tumor must be at least 1.5 cm by imaging
5. Willingness to undergo a screening biopsy, an on-treatment biopsy and surgical resection

Informed Consent:

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

Other Inclusion Criteria:

7. ECOG PS 0 or 1.
8. Adequate Bone Marrow Function, defined as (with no transfusion of blood products or use of hematopoietic growth factors in the 28 days prior to enrollment):
    - ANC ≥1,500/mm^3 or 1.5 × 10^9/L;
    - Platelets ≥100,000/mm^3 or 100 × 10^9/L;

- Hemoglobin ≥9 g/dL.

9. aPTT ≤1.25 × 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.
10. Adequate renal function defined as serum creatinine of ≤1.5 × ULN or an estimated creatinine clearance of ≥60 mL/min by Cockcroft Gault
11. Adequate liver function, defined as:
    - Total serum bilirubin of ≤1.5 × ULN unless the participant has documented Gilbert syndrome. Participants with Gilbert syndrome must have total serum bilirubin ≤3 × ULN.
    - AST and ALT of ≤2.5 × ULN
12. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or cervical carcinoma in situ.
2. 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
    - Symptomatic pulmonary embolism or other clinically significant episode of thromboembolism
3. Any of the following in the previous 6 months:
    - Congenital long QT syndrome
    - Torsade de Pointes
    - Sustained ventricular tachyarrhythmia and ventricular fibrillation
    - Left anterior hemiblock (bifascicular block)
    - Ongoing cardiac dysrhythmias of NCI Common CTCAE ≥Grade 2
    - Atrial fibrillation of any grade (≥Grade 2 in the case of asymptomatic lone atrial fibrillation)

4. Active inflammatory GI disease, chronic diarrhea, known uncontrolled diverticular disease or previous gastric resection or lap band surgery.
5. Cirrhosis meeting criteria for Child Pugh B and C
6. Major surgery (as defined by the Investigator) within four weeks of first dose of study drug
7. History of allergy or reaction to any of the drug components for ARV-471 or anastrozole, including patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
8. Inability to take oral medication without crushing, dissolving, or chewing tablets
9. 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:

10. Prior treatment for breast cancer including systemic therapy (eg, chemotherapy, hormonal therapy), radiation, surgery, or any investigational agents.
11. Any live vaccines within 14 days of planned start of first dose of study drug.
12. Taking the following agents within 14 days of C1D1 unless otherwise specified:
    - Sensitive P-gp substrates or P-gp substrates with narrow therapeutic indices
    - Strong CYP3A4 inhibitors or inducers
    - Any medications with known QT risk, and/or are associated with a risk of Torsades de Pointes, within 7 days of C1D1

Diagnostic Assessments:

13. QTcF >470 msec
14. Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) HBV, HCV, and known HIV or AIDS-related illness.

Other Exclusions:

15. Participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Sponsor approval is required.)
16. Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.
17. Investigator site staff or Sponsor employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

Restrictions regarding lifestyle, activities, and/or diet required for study eligibility and/or participation are listed below. Participants will be instructed by the study staff on the following:

- ARV-471 should be taken together with food at approximately the same time in the morning. Additional instructions on how to take ARV-471 is described in Section 6.1.
- Participants should not consume grapefruit juice as it may interact with ARV-471.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. 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 date of consent, demography, screen failure details, eligibility criteria, and any AEs and SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) must be indicated as such in the IRT system.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times.

5.4.1. Re-testing During Screening

Re-testing of laboratory parameters and/or other assessments within the Screening period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to enrollment is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

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

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the SOC for a given diagnosis, may be considered as non-IPs.

Table 4 Study Product Description

Product Description/ Class and Dosage Form	Potency	IP/ Non-IP	Appearance	Packaging and Labelling	Storage Conditions (per label)
ARV-471 tablets	100 mg	IP	White to off-white oval tablet	IP will be provided in a high-density polyethylene bottle with child-resistant cap. Each bottle will be labelled as required per local regulations.	ARV-471 Patient Bottle Supply (30 count): Store unopened bottle at 2°C to 8°C (36°F to 47°F). Once a bottle is opened, it may be stored at temperatures up to 25°C (77°F) for 8 weeks. Protect from light.
Anastrozole tablets	1 mg	IP	See Pharmacy Manual for full description and Section 6.2		

The label text of the study treatments will comply with Good Manufacturing Practices and national legislation to meet requirements of the participating sites/countries.

6.1. Study Intervention(s) Administered

6.1.1. Administration

Participants will be randomized to one of two treatment arms and will receive study drug for approximately 5.5 months prior to undergoing surgical resection (Table 5). If surgical resection is delayed for non-study drug related reasons, study drug may be continued beyond C6D18 (+14 days) only after discussion with the Medical Monitor. No participant should take study drug dispensed for the trial after surgical resection, and no study drug should be dispensed after surgical resection.

Table 5 Study Treatment

Arm	Study Drug	Daily Dose	Frequency	Route of Administration
A	ARV-471	200 mg	Daily and continuously until day before surgical resection, but no later than C6D18 (+14 days)	Oral
B	Anastrozole	1 mg	Daily and continuously until day before surgical resection, but no later than C6D18 (+14 days)	Oral

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

6.1.1.1. Arm A

Participants in Arm A will use 100 mg strength tablets of ARV-471.

- ARV-471 should be taken by mouth, QD. Participants must be instructed to take ARV-471 with food. Participants should be instructed to take ARV-471 at approximately the same time in the morning. Tablets must be swallowed whole and must not be crushed, chewed, or dissolved.
- ARV-471 should be taken on the day of biopsy and the day the pre-surgical study labs are collected.
- ARV-471 should be administered until the day before surgical resection (no later than C6D18 + 14 days).

Participants taking ARV-471 will self-dose, except for scheduled clinic visits when ARV-471 should be withheld and taken while in the clinic (ie, not at home) under the supervision of study staff.

6.1.1.2. Arm B

Participants in Arm B will use 1 mg strength tablets of anastrozole.

- Anastrozole should be taken by mouth once daily until the day before surgical resection.
- Anastrozole should be taken on the day of biopsy and the day the pre-surgical study labs are collected.
- Anastrozole should be administered until the day before surgical resection (no later than C6D18 + 14 days).
- Additional information on anastrozole can be found in the locally approved product label.

6.2. Preparation, Handling, Storage and Accountability

- The IP should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.
- The IP storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by Arvinas. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed, and Arvinas should be immediately contacted.
- Study treatment not supplied by Arvinas will be stored in accordance with the package insert.
- IP documentation (whether supplied by Arvinas or not) must be maintained that includes all processes required to ensure study treatment is accurately administered. This includes documentation of IP storage, dispensing processes, and administration.
- Further guidance and information for final disposition of unused study treatment are provided in the study Pharmacy Manual.

6.2.1. Preparation and Dispensing

Participants will be dispensed enough tablets of 100 mg of ARV-471 or 1 mg of anastrozole to last until the next scheduled clinic visit by the IRT.

At each visit the participant should bring all bottles/cartons of IP along with their participant dosing diary for review by the site staff.

The number of tablets in each bottle/carton should be recorded before dispensing and on return of bottles/cartons.

6.2.2. Clinical Product Complaints

A Clinical Product Complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies used in a clinical research study sponsored by Arvinas. Any product complaint associated with an IP supplied by the Sponsor are to be reported according to the instructions provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

This is an open-label randomized study. Randomization will be 2:1, and stratification will occur based on the following features of the participant's breast cancer:

- Size of primary breast tumor (T-stage): ≤2 cm, >2 to <5 cm, or ≥5 cm.
- Ki-67 score (assessed locally): <20% or ≥20%

Once screened, the participant will be registered in the IRT system to obtain the participant ID number. Study site users will receive log-in information and directions on how to access the IRT system. Specific instructions for using the IRT will be provided to the investigational site in a separate document.

6.4. Study Intervention Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

Noncompliance is defined as taking less than 80% (providing no required dose interruptions occurred) or more than 120% of assigned study drug during any evaluation period.

For participants receiving ARV-471 (Arm A):
ARV-471 will be administered orally daily with food during each 28-day cycle. On days of scheduled clinic visits, study drug treatment should be withheld and taken while in the clinic (ie, not at home) under the supervision of study staff. Participants will self-dose as described above, with the exception of doses that will be administered at the clinic.

At each visit where additional study drug will be dispensed, the previously dispensed study treatment will be retrieved by the study center and compliance assessed. Participants will be required to return all bottles and remaining tablets of ARV-471, as well as the completed participant diary for drug accountability and compliance. Participants are to complete the study drug diary daily during study participation; documentation of food consumption is

required for C1 only. Participants exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

For participants receiving anastrozole (Arm B):

Anastrozole will be administered orally daily during each 28-day cycle.

At each visit where additional study drug will be dispensed, the previously dispensed study treatment will be retrieved by the study center and compliance assessed. Participants will be required to return all bottles and remaining tablets of anastrozole, as well as the completed participant diary for drug accountability and compliance. Participants are to complete the study drug diary daily during study participation. Participants exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

6.5. Dose Modification and Treatment Discontinuation

The medical monitor or designee must be notified of any hold or dose modification of study drug. See Appendix 6 for suggested actions and follow-up on liver safety.

During the week preceding surgical resection, if a participant experiences any AE that may be related to study drug and may impact surgical risk as per the treating physician, study drug must be discontinued, and surgery should be delayed until AEs have improved enough to allow a safe surgery per the treating investigator.

Dosing for any individual participant may be interrupted (ie, treatment may be temporarily held) if the participant experiences an AE that, in the opinion of the Investigator or Sponsor's medical representative, warrants a dose interruption for that participant's wellbeing. Dosing must be interrupted for certain criteria as discussed in Sections 6.5 and 7. Prior to re-initiating study drug in a participant with a dosing interruption lasting >14 days, the Arvinas medical monitor or designee must be consulted. Periodic study visits to assess safety and laboratory studies should also continue as scheduled or more frequently if clinically indicated during such dosing interruptions. If a participant's treatment is interrupted for more than 21 days, study treatment must be permanently discontinued.

6.5.1. ARV-471

- All Grade 4 AEs related to ARV-471 and considered to be clinically significant per treating investigator require permanent discontinuation of ARV-471.
- For any Grade 3 thromboembolic event or cardiovascular event related to ARV-471, ARV-471 must be permanently discontinued.
- For all ARV-471 related non-hematologic intolerable Grade 2 or Grade 3 AEs, participants should have their dose interrupted until the AE returns to ≤Grade 1 or baseline. Dose reduction should occur per Table 6.
    - Participants may resume treatment in the presence of Grade 2 fatigue.

- For all treatment-related Grade 3 hematologic toxicities, participants should have their dose interrupted until AEs return to Grade ≤2 or baseline. Dose reduction should occur per Table 6.
- In the event of QTcF prolongation (regardless of causality), possible alternate reversible causes (eg, electrolytes, concomitant medications) should be evaluated. If reversible causes are identified, they should be corrected accordingly. If reversible causes are not identified, dose adjustments may be required as described below.
  - Grade 1: no adjustments or additional monitoring is required.
  - Grade 2: no adjustments are required. If the QTcF remains above 480 msec for more than 2 cycles or if Grade 2 QTcF prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the most current ARV-471 IB version, the emerging safety data from ARV-471 trials and the Investigator's best medical judgment. Initiate more frequent ECG monitoring per PI judgement until QTcF ≤480 msec or ≤60 msec change from baseline.
  - Grade 3: withhold ARV-471 treatment until Grade ≤2. If an alternate reversible cause is identified and addressed, resume treatment at the same dose level. If a reversible cause is not identified, reduce ARV-471 by 1 dose level. Initiate more frequent ECG monitoring per PI judgement util QTcF ≤480 msec or ≤60 msec change from baseline.
  - Grade 4: permanently discontinue all study treatment.

Table 6 Dose Reduction – Guidance for Adverse Events Related to ARV-471 (Except QTcF Prolongation)

Intolerable Grade 2 AEs and Grade 3 AEs related to ARV-471[a]	**ARV-471 200 mg dose modification**
First dose reduction	Reduce to 100 mg per day[b, c]
Second dose reduction	Discontinue ARV-471
Any Grade 4 AE related to ARV-471 or any Grade 3 related to ARV-471 thromboembolic events or cardiovascular events	Discontinue ARV-471

Abbreviations: AE=adverse event

a. Grade 3 AEs related to ARV-471 that do *not* require dose reduction:
   - Grade 3 fatigue lasting ≤7 days
   - Grade 3 lymphopenia lasting <72 hours
   - Grade 3 nausea/vomiting/diarrhea lasting ≤72 hours in the absence of maximal medical therapy

b. Depending on the nature of the toxicity and the rapidity of recovery following dose interruption, resumption of the same dose may be considered after the first instance of the related Grade 3 AE or intolerable Grade 2 AE

c. If the participant had a related Grade 2 intolerable AE, and the AE was rapidly reversible, and redosing is not expected to pose a significant risk to the participant, one dose re-escalation of ARV-471 may be considered after consultation with the Medical Monitor.

6.5.2. Anastrozole

Please refer to the current anastrozole approved local product labeling for a summary of the expected safety profile in participants with HR+/HER2− breast cancer, including a full list of all Warnings and Precautions.

- Dose modification of anastrozole is not allowed.
- For Grade 4 AEs related to anastrozole considered to be clinically significant per treating investigator, anastrozole must be permanently discontinued.

Management of AEs related to anastrozole should follow the most up to date local product labeling.

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

The Sponsor will not provide study drugs to participants after they leave the study. Participants should continue their care as normally expected for participants with breast cancer.

6.7. Treatment of Overdose

For this study, any dose of ARV-471 greater than 200 mg daily will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

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

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of ARV-471 (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to the sponsor **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).

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

There is no known antidote for anastrozole overdose. General supportive measures should be taken (refer to anastrozole local product label).

6.8. Prior and Concomitant Therapy

Any vaccine (see COVID information in Appendix 9) or medication (Appendix 8), including over the counter or prescription medicines, vitamins, physiologic replacement doses of systemically administered corticosteroids, and/or herbal supplements that the participant is receiving at the time of enrollment (within 28 days before the time of enrollment) or receives during the study must be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Herbal supplements are not recommended. Other concomitant medications may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, as necessary.

6.8.1. Prohibited Therapy

Known prior medications that exclude a participant from participating in the study are described in the exclusion criteria (Section 5.2).

6.8.1.1. ARV-471

Participants enrolled in this clinical study receiving ARV-471 will not be allowed to receive the following medications, food or herbal supplements (Appendix 8). Unless otherwise specified, these substances should be discontinued at least 14 days prior to starting ARV-471.

- Strong inducers/inhibitors of CYP3A4
- Sensitive P-gp substrates or those with narrow therapeutic indices

- Any medications that are known to prolong the QT interval, and/or are associated with a risk of Torsades de Pointes, within 7 days prior to first dose of ARV-471 and during the study, unless they are being used with caution to treat a drug-related AE when no alternative is available.

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.

H2 blockers (eg, cimetidine, famotidine) or local antacids (eg, aluminum hydroxide, calcium carbonate, bismuth subsalicylate) may be used. Administer ARV-471 ≥2 hours before or after antacids. Administer ARV-471 ≥2 hours before or 10 to 12 hours after H2 blockers.

For additional information regarding concomitant use of ARV-471 with PPIs or H2 blockers, refer to the most current ARV-471 IB version.

6.8.1.2. Anastrozole

Participants enrolled in this clinical study receiving anastrozole will not be allowed to receive medications that are excluded in the anastrozole USPI or local label. Please refer to the USPI or local label for additional information.

6.8.1.3. Other Prohibited and/or Limited use of Anti-tumor/Anti-Cancer or Experimental Drugs, or Procedures

- Other therapies with known anti-cancer effects (including radiation therapy) are prohibited on study prior to surgical resection.

6.8.2. Other Restrictions and Precautions

Participants are not allowed to consume grapefruit juice while receiving ARV-471. Study drugs should be administered as per Section 6.1. Other lifestyle restrictions are described in Section 5.3.

Participation in any interventional or non-interventional investigational studies should be discussed with the Medical Monitor.

6.8.3. Supportive Care

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

6.9. Surgical Resection

Participants should undergo definitive surgical resection approximately 5.5 months after starting study treatment (C6D18 ± 14 days).

Surgery should be performed in accordance with standard local guidelines as agreed upon by the surgeon and participant. Pathological staging (ypT, ypN) must be performed on the resected sample and must be available for data entry and monitoring.

During the week preceding surgical resection, if a participant experiences any AE that may be related to study drug and may impact surgical risk as per the treating physician, study drug should be discontinued (if applicable) and surgery should be delayed until AEs have improved enough to allow a safe surgery per the treating investigator.

After surgery, participants will receive SOC radiation and systemic therapy (chemotherapy, endocrine therapy, etc.) in accordance with local practice guidelines per the treating physician's discretion.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Criteria for Stopping the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to the Sponsor in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

The Sponsor (and/or regulatory agency) reserves the right to discontinue the study for medical and/or administrative reasons at any time.

Conditions that may cause termination of the study in its entirety or an individual study site may include but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to any participant enrolled in the study.
- The Sponsor's decision to suspend or discontinue further testing or evaluation of the drug under study.
- The failure of the Investigator to comply with the approved protocol, appropriate guidelines, and applicable regulations.
- Submission of intentionally or knowingly false information from the Investigator to the Sponsor.

7.2. Discontinuation of Study Intervention

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

- Significant global deterioration of health status requiring discontinuation;

- Objective disease progression, or occurrence of a second malignancy that requires systemic therapy or radiotherapy for treatment.
- Unacceptable toxicity and/or AE warranting discontinuation of ARV-471 or anastrozole as described in Section 6.5.
- Significant protocol violation;
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death;

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for protocol specified follow-up procedures as outlined in the SoA (Section 1.3). The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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.

7.3. Participant Discontinuation/Withdrawal From the Study

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

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

The participant will be permanently discontinued from the study intervention and the study at that time.

If the participant withdraws from the study and also withdraws consent (Section 7.3.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.3.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. If 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.

7.4. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant. Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records

The following actions must be taken if a participant fails to return to 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, he/she will be considered to have withdrawn from the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.

- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions (including but not limited to eligibility) are not allowed.

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

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via

on-site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

8.1. Efficacy Assessments

8.1.1. Disease Response Assessment

8.1.1.1. Imaging and Clinical Assessment

To meet the study's exploratory objectives related to assessment of anti-tumor response, preliminary antitumor activity of ARV-471 and anastrozole, respectively, will be evaluated through tumor assessment imaging, tumor measurement on physical exam, and assessment of pathologic stage/residual disease. Study evaluations will take place in accordance with the SoA (Section 1.3).

8.1.1.2. Radiographic Imaging Assessment

Radiographic imaging (eg, breast ultrasound, breast MRI with contrast, and/or mammogram) is required during Screening, C4D1, and prior to surgical resection. Contrast enhanced breast MRI is the preferred imaging modality. The same imaging method used at baseline must also be used at all post baseline imaging visits (ie, C4D1, within 7 days prior to surgical resection and any unscheduled imaging visits performed to assess the primary breast tumor).

Breast imaging conducted as part of the participant's routine clinical management (eg, ultrasound, MRI, mammogram) and obtained before signing of the ICD may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3). Full staging scans during or prior to screening may be performed, if necessary, at the discretion of the investigator as per SOC.

Tumor imaging response assessment will be performed according to modified RECIST 1.1 criteria. The primary breast tumor must be measurable with a size of at least 1.5 cm (15 mm) in the longest diameter. Additional lesions identified on breast imaging may be followed for response as outlined in Appendix 11.

8.1.1.3. Physical Exam: Caliper-based Measurements

Caliper based measurements of the primary breast tumor must be performed in accordance with the SoA (Section 1.3).

8.1.1.4. Local Pathological Assessment of Tissue from Surgical Resection

Local pathological assessment of the tissue from surgical resection (performed after approximately 5.5 months of treatment), at minimum, should include pathologic stage (ypT and ypN stage) as described in the Laboratory Manual. Pathologic complete response will be defined as the absence of residual invasive cancer on evaluation of the complete breast

specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0/T is ypN0 in the current AJCC staging system).

8.2. Safety Assessments

Safety will be evaluated through AE monitoring, clinical evaluations (ie, vital signs, physical exams, ECGs), and laboratory tests (ie, hematology, serum chemistries).

Any clinically significant changes, in the opinion of the Investigator, noted during abbreviated or final physical examinations, ECG evaluations, and any other safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the appropriate AE page of the eCRF, including information regarding NCI CTCAE v5.0 grade, relationship to study drug, any action taken, date of onset and outcome Appendix 3.

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the breasts, neck/axillary lymph nodes, cardiovascular, respiratory, GI, and musculoskeletal systems. An abbreviated physical examination will be symptom directed.

The physical examination should be performed by the same person each time when possible. Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.4.

8.2.2. Vital Signs

Temperature assessments may be oral or tympanic. BP and pulse measurements will be assessed while the participant is in a sitting position or semi recumbent position (recommended). The same position should be used throughout the study. Manual techniques will be used only if an automated device is not available.

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

8.2.3. Electrocardiograms

Screening ECGs will be single 12-lead ECGs and are not required to be obtained on vendor machines. Starting at C1D1 (pre-dose, baseline), triplicate 12-lead ECGs will be obtained using vendor ECG machines that automatically calculates the heart rate and measures pulse rate, QRS, QT, and QTcF intervals. If screening ECG is obtained on a vendor machine within 96 hours of C1D1 in triplicate, there is no need to repeat the pre-dose ECG testing on C1D1.

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 2 to determine the QTc interval.

All triplicate ECG tracings will be sent electronically to a central ECG laboratory for manual interval measurements. The final ECG reports from the central ECG laboratory should be maintained in the participant's source documentation.

All ECG's must be reviewed by qualified personnel at the site, including verifying that the machine reading is accurate, and that the Fridericia correction formula is applied.

If vendor ECG machine readings return an abnormal ECG finding considered clinically significant by the investigator, the investigator may use their site machine to repeat the assessment. If both the site and vendor machines return an abnormal ECG finding, then the investigator should follow the guidance provided in section 6.5 of the protocol, if applicable. The investigator should consult a cardiologist per their institutional guidelines. The sites should manually upload the ECGs from the site machine into the Clario ERT portal.

Treatment interruption and discontinuation criteria for QTcF prolongation are listed in Section 6.5.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3). The SoA also includes information on allowable windows for testing and windows for screening tests to be used for C1D1. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

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

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

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

No need to repeat clinical laboratory assessments on C1D1 if the baseline assessment was performed within 96 hours prior to that date.

For participant convenience, the blood tests performed during any non-clinic visit (except PK or biomarker collections) day may be performed at the study center or locally (ie, licensed laboratory) and the lab results sent to the Principal Investigator.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the eCRF.

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

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (Section 7.2).

During the active collection period as described in Section 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing

any study related procedure and/or receiving study intervention), through and including a minimum of 30 calendar days after the last administration of the study intervention (ie, study drug treatment or surgical resection, whichever occurs last).

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

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 SAE Report Form.

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Sections 8.3.1 are reported to Pfizer Safety on the SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All AEs and SAEs occurring in a participant during the active collection period which begins after obtaining informed consent, as described in Section 8.3.1, will be recorded on the AE section of the CRF. The recording of non-serious AEs and SAEs will continue until 30 days after last administration of study intervention. Participants who undergo surgical resection >6 weeks after the last dose of study drug will have AEs collected for 42 days after the last dose of study drug.

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

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

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 SAE CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 7.4).

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

Any such exposure to the study intervention under study are reportable to the sponsor within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.
        - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, or skin contact then exposes his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant's partner, the investigator must report this information to Pfizer Safety on the SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last ARV-471 or anastrozole dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a

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

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

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

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

8.3.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female 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 skin contact.

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

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However,

if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.3.5.3. Occupational Exposure

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

8.3.6. 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 the sponsor **only if associated with an SAE**.

8.3.7. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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

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

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

8.4. Pharmacokinetics

For participants receiving ARV-471 only (Arm A), blood sampling for PK analysis will be conducted as specified in Table 3.

8.4.1. Collection of Samples

For participants receiving ARV-471, venous blood samples will be collected for PK. At visits during which blood samples for the determination of multiple aspects of study treatment will be taken, one sample of sufficient volume can be used. Additional samples may be collected at additional time points during the study if agreed upon between the Investigator and the Sponsor (eg, insufficient sample volume to complete testing or to help assess or follow up on any suspected drug-related AE).

The actual date and time (24-hour clock time) of each PK sample will be collected and recorded in the eCRF. The actual dose amount, date, and time of the previous ARV-471 dose and at least one subsequent dose in each PK sample collection day will be recorded. PK samples will be collected, processed, labeled, stored, and shipped as detailed in the study Laboratory Manual.

8.4.1.1. Determination of Drug Concentration

PK samples for the determination of ARV-471 and ARV-473 in plasma will be analyzed using a validated bioanalytical method measuring both ARV-471 and ARV-473 using a chiral assay. Full details of the bioanalytical methods will be described in separate Bioanalytical Reports. All PK samples within the known stability window at the time of receipt by the bioanalytical laboratory will be analyzed. Plasma samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays and/or to investigate the presence of ARV-471 and/or its metabolites. Samples collected for analyses of concentrations of ARV-471 and ARV-473 may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.4.1.2. Determination of Pharmacokinetic of Individual Participants

Plasma concentrations of ARV-471 and ARV-473 from sparse PK sampling will be analyzed using population PK approach to determine exposure and clearance parameter values for individuals. The effects of concomitant medications, participant demographics (eg, race, age, body size), and intrinsic factors such as renal or hepatic functions on ARV-471 and ARV-473 will be explored. A separate population PK report may be issued following the completion of the study.

8.5. Genetics

8.5.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.6. Biomarkers

Local assessment of Ki-67 will be used for randomization.

On study Ki-67 and ER testing will be conducted in certified Clinical Laboratory Improvement Amendments central testing laboratories. Ki-67 expression will be measured by IHC. ER expression will be measured by quantitative immunofluorescence. These analyses will be done in a blinded manner at the central laboratories.

Analysis of additional PD and other biomarkers thought to play a role in breast cancer or drug response may also be performed including, but not limited to, PgR expression, [redacted]

Samples may be stored for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to the study drugs.

8.6.1. Mandatory Tumor Biopsies

Tumor samples for PD endpoints and other biomarker research that should be collected from participants are:

- Screening: 3 to 5 core biopsies from the primary breast tumor
- On-treatment biopsy on C1D15 (+5 days): 3 to 5 core biopsies from the primary breast tumor
- Tumor samples from surgical resection (after approximately 5.5 months of treatment): equivalent of 3 to 5 core biopsies, at minimum

Details on biopsy collection and processing are provided in the Laboratory Manual.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

9.1.1. Multiplicity Adjustment

This is a Phase 2 POC study designed to generate data informing future studies about ARV-471. There are no plans for formal comparisons or hypotheses testing. There is no need for Type I error control.

9.1.2. Estimands

9.1.2.1. Primary Estimands

The primary estimand of this study is defined as the percent change in Ki-67 expression between baseline and C1D15 tumor biopsies observed from each Arm, respectively. Descriptive statistics will be provided to evaluate the effects of ARV-471 and anastrozole, respectively, on Ki-67 expression in tumors after two weeks of treatment. No comparisons between the treatment arms are planned.

Treatments: ARV-471 (Arm A) and anastrozole (Arm B)

Population: post-menopausal women with newly diagnosed and treatment naive ER+/HER2– breast cancer that is amenable to definitive surgical resection. Participants must also have tumor that is at least 1.5 cm by imaging due to biopsy requirements for this study. The primary analysis regarding Ki-67 expression will be performed in all enrolled participants who received at least one dose of study treatment and had evaluable Ki-67 measurements from baseline and C1D15 visits.

Variable: the log-transformed Ki-67 after approximately two weeks of treatment as a percentage of the baseline value, ie, the ratio between the Ki-67 measurements obtained from C1D15 visit and baseline.

Intercurrent events: only participants with evaluable Ki-67 results from baseline and C1D15 visits will be included in the primary analysis. No participants will be censored or excluded due to any reasons other than missing Ki-67 data.

Population-level summary: the log-transformed percentage Ki-67 will be modelled using a GLM. Refer to Section 9.3.2 and the SAP for more details.

9.1.2.2. Secondary Estimands

There are no key secondary endpoints defined for this study. No estimands are defined for any of the secondary or exploratory endpoints. Statistical analyses for the secondary and exploratory endpoints are described in Section 9.3 and in the SAP.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full Analysis Set	All enrolled participants who were randomized. Participants are analyzed according to the treatment they have been randomized to.
Safety Analysis Set	All enrolled participants who receive at least 1 dose of study intervention.
Ki-67 Evaluable Set	All enrolled participants who were randomized and received at least one dose of study treatment and had evaluable Ki-67 measurements from baseline and C1D15 visits.

Participant Analysis Set	Description
Pharmacodynamic/Biomarker Analysis Set(s)	The Pharmacodynamic /Biomarker analysis population is defined as all enrolled participants with at least 1 of the Pharmacodynamic /Biomarkers evaluated at pre and/or post dose.
Pharmacokinetic Analysis set(s)	**PK Concentration Analysis Set** The PK Concentration Analysis Set includes all participants in the Safety Analysis Set who have at least one plasma concentration (including those below the limit of quantification) for ARV-471, or ARV-473. **PK Parameter Analysis Set** The PK Parameter Analysis Set will include all participants in the Safety Analysis Set who have at least one PK parameter of interest for ARV-471, or ARV-473 (C_{max} or AUC). **PK Pre-Dose Concentration (C_{trough}) Analysis Set** The PK Pre-Dose Concentration Analysis Set will include all participants in the Safety Analysis Set who have at least one evaluable C_{trough} and within the allowable time window following treatment for ARV-471 or ARV-473. The allowable time window for the PK Pre-Dose sample is defined in the following way: • Dosing time from the day prior to PK sample collection is known. The allowable time window is the period of time between 22 hours after dosing on the day prior to the sample collection, and 30 minutes after dosing on the day of sample collection. • Dosing time from the day prior is not available. The allowable time window is the period of time between 2 hours before dosing and 30 minutes after dosing on the day of sample collection.

9.3. Statistical Analyses

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

9.3.1. General Considerations

No formal comparisons between ARV-471 and anastrozole or hypotheses testing are planned for this study. Descriptive statistics (including point estimates and two-sided CIs) will be provided for all parameters of interest. For information purposes, all the 2-sided CIs will be reported on both 80% and 95% confidence levels.

Statistical analyses for the primary and secondary endpoints are summarized below and in the SAP.

9.3.2. Primary Safety/Efficacy Analyses

Ki-67 expression will be assessed by immunohistochemical staining in a central laboratory.

Analysis of Ki-67 reduction will be based on a Ki-67 evaluable population. The log-transformed Ki-67 after approximately 2 weeks of treatment as a percentage of the baseline value, ie, the ratio between the Ki-67 measurements obtained from C1D15 visit and baseline, will be modelled using a GLM, with both stratification factors (ie, baseline Ki-67 score and the tumor size) and treatment as covariates. Treatment effects for each arm will be summarized using the LSM and their two-sided CIs on the log scale. In addition, for easier interpretation of the data, the treatment effects will be back transformed and expressed as the geometric means and their CIs on the original percentage scale by treatment arm. The percent change, in other words, relative reduction, of Ki-67 after 2 weeks of treatment will also be reported as the complement of the ratio between the Ki-67 measurement from C1D15 and baseline, ie, 100% × (1-Ki-67 from C1D15/Ki-67 from baseline). Similar modeling will be applied to ER data.

9.3.3. Secondary Endpoint(s)/Estimands Analysis

pCR is defined as no invasive cancer in the breast and sampled axillary lymph nodes following completion of neoadjuvant systemic therapy. The rate of pCR will be reported for each arm using both point estimates and exact Wilson CIs. Odds ratios between the treatments will also be reported using mPEPI score derived from factors assigned a numerical score following NET, including Ki67 expression in the surgical specimen, pathologic tumor size, and lymph node status. The proportion of participants achieving mPEPI score 0 after treatment will be evaluated.

To support secondary objective of evaluating clinical and pathologic response, binary or categorical endpoint such as pathologic stage, pCR, and participants with mPEPI score zero at the time of surgical resection (C6D18 ± 14 days), rates of BCS, radiographic response per mRECIST in the primary tumor during Cycle 6 will be summarized and the estimated rate will be computed by treatment arm along with the exact CI using Wilson method; For caliper-based response on C6D1, best percentage change from baseline will be graphed by treatment arm. All clinical and pathologic response will be listed for randomized participants by treatment arm.

9.3.4. Tertiary/Exploratory Endpoint(s)

CCCA at Week 2 is defined as Ki67 score ≤2.7%. An estimate of the difference in the observed CCCA rates and corresponding 80% as well as 95% CIs will be calculated. Odds ratios between the treatments adjusted for the stratification factors through the Cochran-Mantel-Haenszel method will be provided along with their CIs.

9.3.5. Subgroup Analyses

Summaries of the primary endpoint will be presented for subgroups defined by the following criteria:

- Size of primary breast tumor (T-stage): ≤2 cm, >2 to <5 cm, or ≥5 cm

- Baseline Ki-67 score (assessed locally): <20% vs ≥20%

Other factors will be considered if the observed data imply potential findings of clinical interest. Results of the primary analysis will be reported within each subgroup. Forest plots will be provided.

9.3.6. Other Safety Analyses

All safety analyses will be performed on the safety population. Descriptive statistics of safety will be presented using NCI CTCAE v5.0. All TEAEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade per NCI CTCAE v5.0 criteria. The extent of exposure including number of doses, duration of treatment, and dose modifications will be summarized by treatment arm. A summary of deaths with reasons will be provided for all treated participants.

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

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

9.4. Sample Size Determination

There are no plans for formal comparisons between ARV-471 and anastrozole. No power calculations are needed. Approximately 150 participants will be randomized to the two treatment arms in 2:1 ratio (100 participants to the ARV-471 arm and 50 participants to the anastrozole arm). These numbers were chosen to provide meaningful information about the primary endpoint, ie, changes (on-treatment C1D15 vs baseline) in Ki-67 expression levels after approximately 2 weeks of treatment with ARV-471 and anastrozole, respectively.

Table 7 and Table 8 provide a list of probable scenarios demonstrating the width of the CIs for the primary endpoint under the assumption that 80% (ie, n=120) of the randomized participants will provide valid Ki-67 measurements from both their baseline and C1D15 visits. Table 7 indicates that the width of the 80% CIs of the mean percentage Ki-67 after 2 weeks of treatment by ARV-471 will not exceed 14% and the width of the 95% CIs will not exceed 21.6% if the mean percentage of the corresponding baseline values after 2 weeks of treatment ranges from approximately 20% to 40%. The planned sample size will provide

estimates for the treatment effect in terms of the reduction of Ki-67 with reasonable precision.

Table 7 Confidence Intervals for Mean Percentage of Baseline Value in Ki-67 After Two Weeks

Number of participants/arma	Mean percentage Ki-67 in two weeksb	SD of log-transformed percent change in Ki-67c	80% CId	95% CId
100 (80 evaluable)	20%	1.0	(17.3%, 23.1%)	(16.0%, 25.0%)
	30%		(26.0%, 34.7%)	(24.0%, 37.5%)
	40%		(34.6%, 46.2%)	(32.0%, 50.0%)
	20%	1.2	(16.8%, 23.8%)	(15.3%, 26.1%)
	30%		(25.2%, 35.7%)	(23.0%, 39.2%)
	40%		(33.6%, 47.6%)	(30.6%, 52.2%)
50 (40 evaluable)	20%	1.0	(16.3%, 24.6%)	(14.5%, 27.5%)
	30%		(24.4%, 36.9%)	(21.8%, 41.3%)
	40%		(32.5%, 49.2%)	(29.1%, 55.1%)
	20%	1.2	(15.6%, 25.6%)	(13.6%, 29.4%)
	30%		(23.4%, 38.4%)	(20.4%, 44.0%)
	40%		(31.2%, 51.2%)	(27.3% 58.7%)

a. Approximately 100 participants will be enrolled to the ARV-471 arm with 80 participants providing valid Ki-67 data. Approximately 50 participants will be enrolled to the anastrozole arm with 40 participants providing valid Ki-67 data.
b. Percentage Ki-67 in two weeks is defined as the ratio between Ki-67 reported from C1D15 visit and baseline, respectively.
c. Ki-67 measurements are assumed to follow a log-normal distribution. The CIs are generated using the quantiles of the standard normal distribution on the log scale. Various values for the SD of the log-transformed Ki-67 percent change are provided to mimic the variability reported in the coopERA study (Hurvitz 2022a).
d. The CIs are presented in the original percentage scale through exponential-transformation of the Cis generated using the log-transformed Ki-67 data.

Table 8 Confidence Intervals for the Ratio Between the Mean Percentage of Baseline Values for Ki-67 Observed from ARV-471 and Anastrozole Arms (Ki-67 Evaluable Participants N=120)

Mean percentage Ki-67 with ARV-471a	Mean percentage Ki-67 with anastrozolea	SD of log-transformed percentage Ki-67b	Difference of mean percentage Ki-67 (anastrozole – ARV-471)	80% CI for the ratio of mean percentage Ki-67c	95% CI for the ratio of mean percentage Ki-67c
20%	30%	1.0	10%	(1.17, 1.93)	(1.02, 2.20)
30%	40%			(1.71, 1.04)	(0.91, 1.96)
20%	30%	1.2		(1.11, 2.02)	(0.95, 2.38)
30%	40%			(0.99, 1.80)	(0.84, 2.11)
20%	28%	1.0	8%	(1.09, 1.80)	(0.95, 2.05)
30%	38%			(0.99, 1.63)	(0.86, 1.86)
20%	28%	1.2		(1.04, 1.89)	(0.88, 2.22)
30%	38%			(0.94, 1.71)	(0.80, 2.01)

20%	25%	1.0	5%	(0.97, 1.60)	(0.85, 1.83)
30%	35%			(0.91, 1.50)	(0.80, 1.71)
20%	25%	1.2		(0.93, 1.69)	(0.79, 1.98)
30%	35%			(0.86, 1.57)	(0.74, 1.85)

a. Assume the relative reduction in Ki-67 attributed to ARV-471 exceeds the reduction attributed to anastrozole by 5%, 8% and 10% respectively in various scenarios.
b. Assume the same SD for the log- transformed percent change in Ki-67 in either arm.
c. The ratio is defined as the mean percentage Ki-67 with anastrozole divided by the mean percentage Ki-67 with ARV-471. A ratio above unity (1) is in favor of ARV-471.

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, applicable European regulations, and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study center at which the Investigator has not signed the protocol.

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, the sponsor should be informed immediately.

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate

hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 30 days from the previous ICD signature date.

10.1.4. Data Protection

The Sponsor or its representative will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, the Sponsor or representative physician or an Investigator might know a participant's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

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 securely to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

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

10.1.5. Committees Structure

Please refer to Section 4.4.

10.1.6. Dissemination of Clinical Study Data

The results of the study should be reported within one year from the end of the clinical trial. Irrespective of the outcome, the Sponsor will submit to the appropriate database a summary of the results of the clinical trial within one year from the end of the clinical trial. It shall be

accompanied by a summary written in a manner that is understandable to laypersons (where applicable).

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.

The investigator must ensure that the CRFs are securely stored at the study site to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

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.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

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

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

Criteria for Stopping the Study

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;

- Discontinuation of further study intervention development.

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

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

10.1.10. Publication Policy

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

The data generated by this study are confidential information of the Sponsor. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel for study related medical questions or problems, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) the sponsor Call Center number.

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

10.2. Appendix 2: Clinical Laboratory Assessments

The tests detailed in Table 9 will be performed by the local laboratory. The results of each test must be entered into the eCRF. Investigators must document their review of each laboratory safety report.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 9 Core Lab Tests

Laboratory Test	Notes
Hematology	
Hemoglobin	Database should be constructed to allow capture of differential counts as percent and absolute values but only one or the other should be used by the site to collect data. Results will be reported as absolute values after conversion and graded according to the CTCAE criteria.
Hematocrit	
Red blood cell count	
Platelet count	
WBC	
Absolute Neutrophils	
Absolute Lymphocytes	
Absolute Monocytes	
Absolute Eosinophils	
Absolute Basophils	
Chemistry	
ALT	For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, Tbili, direct bilirubin, GGT, PT/INR, and alkaline phosphatase
AST	
Tbili	
Alk Phos	
Sodium	
Potassium	
Magnesium	
Chloride	
Total Calcium	
Ionized calcium	If clinically indicated
BUN or Urea	
Creatinine	
Uric Acid	
Glucose (non-fasted)	
Albumin	
Phosphorus or Phosphate	
Creatine kinase	At screening and if clinically indicated
Creatine kinase MB fraction will be performed	If clinically indicated
Amylase	
Lipase	
Direct bilirubin	If clinically indicated
Carbon dioxide (bicarbonate)	

Laboratory Test	Notes
Coagulation	
PT/INR	
PTT/APTT	
Urinalysis	
Leukocyte esterase	
Protein	
Urine bilirubin	
Urobilinogen	
Ketones	
pH	
Nitrites	
Specific Gravity	
Glucose (qual)	
Blood (qual)	
Microscopy (if clinically indicated)	Only if urine dipstick is positive for blood, protein, nitrates, or leukocyte esterase.
Viral Serology	
HIV I and II	Historical results obtained within 28 days of enrollment may be used to determine eligibility
Hepatitis B virus (HBV)	
Hepatitis C virus (HCV)	

Note: Details of dosage modification, stopping criteria, and follow up of abnormal test results are provided in Section 6.5, Section 7, and Section 8.2.4.

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- 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.

10.3.2. Definition of an SAE

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

a. Results in death

b. Is life-threatening

The 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 detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization 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,

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:
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 an IP of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to an IP. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.
g. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE. • Grade 5 (see Assessment of Severity in Section 10.3.3).

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

AE and SAE Recording/Reporting
The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure. It should be noted that the SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical

terminology and the same AE term should be used on both the CRF and the SAE Report Form for reporting of SAE information.

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

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to the sponsor using SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to the sponsor using the SAE Report Form.
** **EDB** is reported to the sponsor using the SAE Report Form which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to the sponsor using the SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. 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 the sponsor.

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

Assessment of Severity

The investigator will make an assessment of severity for each AE reported during the study and assign it to 1 of the categories listed below (as defined by the NCI CTCAE system). An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

GRADE	Clinical Description of Severity
1	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 his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is** very **important that the investigator always make an assessment of causality** for **every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting

Every SAE, regardless of suspected causality, occurring during the SAE reporting period per Section 8.3.1, must be immediately reported to Pfizer drug safety unit (DSU) via CT SAE Report Form, without undue delay and under no circumstance later than 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE leading to death, and recurrent episodes must be immediately reported as follow-up to the original episode no later than 24 hours after the Investigator receives the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event in a new individual case safety report.

Information about the SAE will be collected and recorded on the Pfizer CT SAE Report Form, as well as in the Trio Electronic Data Capture (EDC) system. All applicable sections of the form must be completed and consistent in order to provide a clinically thorough report.

SAE will be reported on a paper CT SAE Report Form to the relevant Pfizer DSU via:

DSU	Country Name	Adverse Event Contact Email	FAX N°
GERMANY	GERMANY	[redacted]	

RUSSIAN FEDERATION: Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan	GEORGIA	[redacted]
SPAIN: Andorra	SPAIN	
UNITED STATES: American Samoa, Guam, Northern Mariana Islands, Puerto Rico, United States Virgin Islands and United States Minor Outlying Islands	UNITED STATES	

Detailed instructions regarding the SAE submission process are to be found in the Investigator folder provided to each site.

The Investigator, or designated party, should notify the appropriate IRB/EC of SAEs occurring at the study site and other AE reports received from the Sponsor, in accordance with local procedures and statutes.

The Investigator, or designated party, should notify the appropriate IRB/EC of SAEs occurring at the study site and other AE reports received from the Sponsor, in accordance with local procedures and statutes.

10.4. Appendix 4: Contraceptive and Barrier Guidance

All participants enrolled in this study will be post-menopausal females as defined in Section 5.1, and thus contraceptive and barrier guidance does not apply.

10.5. Appendix 5: Genetics

Not applicable to this study.

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

Potential Cases of Drug Induced liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede Tbili elevations (>2 × ULN) by several days or weeks. The increase in Tbili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and Tbili values will be elevated within the same laboratory sample). In rare instances, by the time Tbili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST or ALT in addition to Tbili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

Preexisting values of Tbili above the normal range: Tbili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and Tbili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should

include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and Tbili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AE

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

ECG Findings That May Qualify as Serious AE

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

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.

- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

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

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

Participants should **not** receive the following while participating in trials with ARV-471 (unless utilized with caution to treat a drug-related AE when no alternative is available).

Note: These lists are examples and are not intended to be exhaustive.

- Examples of sensitive P-gp substrates and P-gp substrates with narrow therapeutic indices:

P-gp substrates with narrow therapeutic indices:	dabigatran etexilate, digoxin, fexofenadine, apixaban, rivaroxaban

- Examples of strong CYP3A4 inhibitors and inducers

Strong CYP3A4 inhibitors:	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole clarithromycin, idelalisib, nefazodone, nelfinavir
Strong CYP3A inducers:	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

- Examples of known QT prolonging drugs:

Known QT prolonging drugs:	aclarubicin, amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, cesium chloride, chloroquine, chlorpromazine, chlorprothixene, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, hydroquinidine, hydroxychloroquine, ibogaine, ibutilide, levolfoxacin, levomepromazine (methotrimeprazine, levomethdyl acetate, levosulpiride, meglumine antimoniate, mesoridazine, methadone, moxifloxacin, nifekalant, ondansetron, oxaliplatin, papaverine HCl (Intracoronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sertindole, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terfenadine, terlipressin, terodiline, thioridazine, vandetanib

References:

Examples of sensitive P-gp substrates and those with narrow therapeutic indices

- https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-tablesubstrates-inhibitors-and-inducers
  - Table 5-1: Examples of clinical substrates for transporters (for use in clinical DDI studies and/or drug labeling) (12/03/2019)

Examples of Strong CYP3A4 inhibitors (eg, itraconazole) and inducers (eg, rifampin)

- https://drug-interactions.medicine.iu.edu/MainTable.aspx
- https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-tablesubstrates-inhibitors-and-inducers
  - Table 3-2: Examples of clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (03/06/2020)
  - Table 3-3: Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (12/03/2019)

Examples of known QC prolonging drugs

- https://www.crediblemeds.org/index.php

10.9. Appendix 9: Alternative Measures During Public Emergencies

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

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

10.9.1. Eligibility

While SARS-CoV2 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-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Participants with active infections are excluded from study participation as per exclusion criteria, (Section 5.2). When the infection resolves, the participant may be considered for re-screening.

10.9.2. Telehealth Visits

The use of Video TeleMed Visits during public emergencies will be acceptable in the following cases:

Visits where only AE assessment and routine blood samples, which may be performed locally, are required and the results are received and reviewed by the Investigator prior to the TeleMed visit with the participant.

Visits occurring on Day 1 of Cycle 3 and beyond may be done via TeleMed if the participant did not have any significant toxicities requiring re-assessment at the previous in-person visit and has not reported any new significant toxicity in the interim. The same requirement for receiving and reviewing laboratory results as noted in the previous bullet point also apply in this case.

Other study visits should be maintained as in-person clinic visits unless local, governmental, or other restrictions are in place that prohibit travel or in-person clinic visits. In such cases, the Sponsor should be advised in advance, where possible, that a TeleMed visit will be used.

The use of alternate or local labs and/or imaging centers is allowed at the discretion of the Investigator. Use of an alternate imaging center should have Sponsor approval prior to use.

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

10.9.3. Study Intervention

Participants who cannot be seen in clinic due to quarantine requirements or other limitations due to public health emergencies may receive IP shipped, utilizing a secure delivery method with signature required, directly to their home address. The site is to confirm receipt of the

shipment with the participant, document participant compliance and the need for direct shipment to the participant.

10.9.4. Adverse Events and Serious Adverse Events

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

10.9.5. Treatment for COVID While on Study

If a participant tests positive for COVID and has respiratory or other symptoms requiring medical intervention or hospitalization, ARV-471 or anastrozole is to be discontinued. All participants may receive any available therapy to treat their symptoms, including treatments authorized by the FDA for emergency use for COVID-19. Clear documentation must be provided in the participant's medical record and their eCRF regarding all therapy received as well as all AEs related to COVID and its treatment.

10.9.6. Guidance for COVID vaccine administration

10.9.6.1. For Participants Who Have Not Initiated Study Treatment

It is recommended that they should receive the second dose of vaccine at least five days prior to initiation of study treatment. In addition, they should have completely recovered from any side effects related to administration of the vaccine before starting study treatment.

10.9.6.2. For Participants Already on Study Treatment and Beyond Cycle 1

Participants who are already receiving study treatment and beyond Cycle 1, may receive the vaccine as it becomes available to them. Please carefully document any AEs that occur related to the vaccine administration and advise the Sponsor of any significant reactions that occur.

10.10. Appendix 10: Eastern Cooperative Oncology Group Performance Status

Developed by the Eastern Cooperative Oncology Group (ECOG), Robert L. Comis, MD, Group Chair

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up an about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken M, Creech R, Tormey D. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

10.11. Appendix 11: Radiological Imaging Assessment: modified RECIST 1.1

The antitumor activity of study treatment will be assessed according to modified RECIST 1.1 adapted from Eisenhauer 2009. Breast tumor imaging will be performed following the SOA, tumor imaging data will be entered into the CRF and tumor imaging response derived per modified RECIST 1.1 as described in this appendix. RECIST 1.1 modifications are outlined in Table 10.

Consistent imaging methods must be used for all imaging visits for the same participant.

Table 10 RECIST 1.1 Modifications

Requirement	RECIST 1.1	Modified RECIST 1.1	Reasoning
Imaging Modality	Contrast enhanced CT/MRI body imaging	Contrast enhanced breast MRI Breast Ultrasound Breast Mammography	Study protocol is assessing treatment effect on breast cancer primary tumor
Measurable Disease	Non-nodal disease minimum size is 10 mm in the longest diameter Lesions can be identified from all organ groups	Primary breast lesion minimum size is 1.5 cm (15 mm) in the longest diameter Additional lesions identified on breast imaging (meeting RECIST 1.1 criteria) may be identified and followed as target lesions	Study protocol is assessing treatment effect on breast cancer primary tumor and required imaging is breast imaging
Non-measurable Disease	Lesions can be identified from all organ groups	Lesions identified on breast imaging that do not meet target lesion criteria	Study protocol is assessing treatment effect on breast cancer primary tumor and required imaging is breast imaging
Irradiated lesions	Previously irradiated lesions may be identified as a measurable lesion if the lesion demonstrates progressive disease	Exclusion criteria prohibits prior radiation treatment	Protocol exclusion criteria

10.11.1. Imaging Requirements

Radiographic imaging (eg, breast ultrasound, breast MRI with contrast, and/or mammogram) is required during Screening, C4D1, and within 7 days prior to surgical resection. Contrast enhanced breast MRI is the preferred imaging modality. The same imaging method used at baseline must also be used at all post baseline imaging visits (eg. C4D1, within 7 days prior to surgical resection and any unscheduled imaging visits performed to assess the primary breast tumor). A change in imaging technique (ie, modality) could result in lesion status being not evaluable.

Breast imaging conducted as part of the participant's routine clinical management (eg, ultrasound, MRI, mammogram) and obtained before signing of the ICD may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

The primary breast tumor must be measurable with a size of at least 1.5 cm (15 mm) in the longest diameter. Tumor imaging response assessment will be performed according to mRECIST 1.1 criteria.

During, or prior to screening, full staging scans may be performed, if necessary, at the discretion of the investigator as per SOC. Any identified lesions may be followed as a non-target lesion with consistent repeat imaging.

10.11.2. Modified RECIST 1.1 Disease Assessment

10.11.2.1. Measurable Lesions at Baseline

Measurable Lesions: Lesions identified on breast imaging that can be accurately measured in at least 1 dimension, are reproducible and represent study disease.

- Primary breast lesion with a minimum measurement of 1.5 cm (15 mm) in the longest diameter measurement
- A non-nodal (not primary breast tumor) lesion that can be accurately measured at baseline with a minimum measurement of 10 mm in the **longest diameter measurement** and is suitable for accurate repeated measurements.
- A pathological (malignant) lymph node that can be accurately measured at baseline with a minimum measurement of 15 mm in the **short axis measurement** are considered measurable and assessable as target lesions.
- If imaging is breast MRI and MRI slice thickness is more than 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan. Up to 5 lesions per organ type (eg, breast tissue, lymph nodes, chest wall) may be recorded.
- Soft tissue component of bone may be identified as target lesion if the soft tissue component measurement is at least 10 mm (the lesion must be in a location that will be included in the field of view on subsequent breast imaging).

10.11.2.2. Nontarget Lesions at Baseline

Non measurable disease includes all other lesions, (or sites of disease) identified on breast imaging not recorded as target lesion as well as non-nodal lesions that are too small to be considered measurable and truly non measurable lesions that represent study disease, such as pathological lymph nodes with short axis measurement between 10 mm and 14.9 mm, chest wall disease and/or osseous bone lesions.

Lesions identified on staging standard of care imaging may be entered as non-target lesion and followed for response assessment.

10.11.2.3. Normal Sites of Disease

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

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

10.11.2.4. Recording Modified RECIST 1.1 Tumor Assessments

All sites of disease should be assessed at baseline. Baseline assessments should be done as close as possible to the start of study treatment and within 28 days prior randomization. If baseline assessment is inadequate or missing, subsequent statuses generally should be recorded as not evaluable until progressive disease is identified.

Target Lesions

Target lesions should be selected based on size (longest lesions) and suitability for accurate repeated measurements. The site and location of each target lesion will be recorded as well as the longest diameter for each non-nodal lesion and the shot axis diameter for each pathological lymph node that meet the size criteria for a target lesion. The SOD of the target lesions at baseline will be the basis for comparison to post baseline imaging assessments and the post baseline SOD.

Target lesions will be assessed post baseline for lesion status and measurements recorded. The SOD will be compared to baseline SOD and to nadir (smallest SOD on study) SOD to derive the target lesion response (see Table 11).

Post-Baseline Target Lesion Special Considerations:

- Actual measurements for target lesion (nodal and non-nodal) should continue to be recorded (including nodes that have reduced to normal size).
- Target lesions (nodal and non-nodal) that are too small to measure should be considered as a default value of 5 mm.
- Target lesions (nodal and non-nodal) that are considered to have disappeared should be recorded as 0 mm (including nodes that are no longer visible on imaging).
- If a target lesion cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- If a target lesion disappears (or reduces to normal size for lymph node) and reappears at a subsequent time point, the lesion should continue to be measured and included in the SOD. In the event that all target lesions achieved CR status, the lesion reappearance would be considered as progressive disease at the time of reappearance.
- If 2 or more target lesions coalesce (merge), the measurement of the coalesced mass is recorded and used in the SOD.
- If a large target lesion splits into 2 or more parts, each part is recorded, and the sum of the parts is used in the SOD.
- When a target lesion has had any intervention (ie, radiotherapy, embolization, surgery) during the study, the size of the target lesion should still be provided when possible. If the invention results in the target lesion measurement not possible, the target lesion should be identified as Not Evaluable.

- If one or more target lesion is Not Evaluable, and the sum of diameters meets the criteria for progressive disease, progressive disease overrides not evaluable as the target lesion response.
- Target lesion response of progressive disease requires 20% increase in the SOD of all target lesions AND a minimum absolute increase of 5 mm in the SOD.

Non-Target Disease

NTLs will be identified at baseline. Measurements are not required for these lesions, but their status will be followed at post baseline visits.

At each post-baseline visit the NTL status (ie, Present, Absent, Not Evaluable, Not Assessed) will inform the NTL response. To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of treatment. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. See Table 12 for NTL overall response at each assessment.

New Lesions

At each post baseline visit, imaging will be assessed for any new lesions. Details of any new lesions will also be recorded with the date of assessment and lesion location/description. The presence of one or more new lesions is assessed as progressive disease. A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

10.11.3. Disease Response Status at Each Imaging Assessment

The timepoint assessment will include deriving the Target Lesion Response, Non Target Lesion Response and the Overall Response based on the lesion status of the target, non-target and/or new lesions assessed at the post-baseline imaging visit.

For target lesion response of Complete Response/Partial Response, imaging must be evaluable, with all anatomy covered, and with no target lesion with status of Not Evaluable/Not Assessed.

10.11.3.1. Target Disease Response Status

Target lesion response definitions for each imaging assessment:

Complete Response (CR)	Complete disappearance of **all t**arget lesions with the exception of nodal disease. All target lymph nodes must decrease to normal size (short axis <10 mm).
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	If the SOD does not derive PD, and: • One or more of the target lesions have not been assessed; OR • One or more target lesion cannot be measured accurately due to poor technical quality; OR • One or more target lesions were excised or irradiated and have not reappeared or increased; OR • Imaging modality or assessment method is inconsistent with baseline assessment

10.11.3.2. Nontarget Disease Response Status

NTL response definitions for each imaging assessment:

Complete Response (CR)	Disappearance of all NTL since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-Complete Response/Non-Progressive Disease	Persistence of one or more non target lesions
Progressive Disease (PD)	Unequivocal progression of existing NTL. Unequivocal progression may be due to progression in one lesion only or in several lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy.
Not Evaluable (NE)	An overall non-target assessment cannot be made at this visit based on one or more of the following: • One or more of the NTL have not been assessed; OR • One or more NTL cannot be assessed due to poor technical quality; OR • One or more NTL were excised or irradiated and have not reappeared or increased; OR

	• Imaging modality or assessment method is inconsistent with baseline assessment and impacts the ability to accurately assess the disease status

10.11.3.3. New Lesions

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

New lesion definition for each imaging assessment:

Yes	Definitely present
No	Not present, or uncertain

10.11.3.4. Overall Response at Each Imaging Assessment

Table 11 RECIST 1.1 Overall Response at Each Assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD, NE	No	PR
SD	Non-PD, NE	No	SD
NE	Non-PD, NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NA	Non-CR/Non-PD	No	Non-CR/Non-PD
NA	NA	No	NED
NA	NE	No	NE

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; NE=not evaluable/not all assessed/missing; NED=no evidence of disease (relevant when no TL and NTL at baseline); NA=Not Applicable (relevant when no TL and/or NTL at baseline); NTL=non-target lesion; TL=target lesion

Table 12 Non-Target Disease Only RECIST 1.1 Overall Response at Each Assessment

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
NE	No	NE
Unequivocal Progressive Disease	Yes or No	PD
Any	Yes	PD

CR=complete response; PD=progressive disease; NE=Not Evaluable/Not Assessed

10.12. Appendix 12: Abbreviations

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

Abbreviation	Term
AE	adverse event
AI	aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
Alk Phos	alkaline phosphatase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
BCRP	breast cancer resistance protein
BCS	breast conserving surgery
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C	Cycle
C1D1	Cycle 1 Day 1
CAP	College of American Pathologists
CBR	clinical benefit response
CCCA	complete cycle cell arrest
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK1α	casein kinase 1α
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID	coronavirus disease
CRF	case report form
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CYP	cytochrome P450
D	Day
DC_{50}	half-maximal degradation concentration

Abbreviation	Term
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSU	drug safety unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
ER	estrogen receptor
ER+	estrogen receptor positive
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GI_{50}	half-maximal growth inhibition
GLM	generalized linear model
GLP	good laboratory practices
GSPT1	G1 to S Phase Transition 1 gene
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR+	hormone receptor positive
IB	investigator's brochure
IC_{50}	half-maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
LFT	liver function test
LSM	least square means

Abbreviation	Term
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
mPEPI	modified Pre-Operative Endocrine Prognostic Index
mRECIST	modified Response Evaluation Criterion in Solid Tumors
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not applicable
NCI	National Cancer Institute
NE	not evaluable/not all assessed/missing
NED	no evidence of disease (relevant when no TL and NTL at baseline)
NET	neoadjuvant endocrine therapy
NOAEL	no-observed-adverse-effect level
NOD/SCID	nonobese diabetic/severe combined immunodeficiency
NTL	non-target lesion
nsAI	nonsteroidal aromatase inhibitor
ORR	objective response rate
pCR	pathologic complete response
PD	pharmacodynamics(s)
P-gp	p-glycoprotein
PgR	progesterone receptor
PK	pharmacokinetic(s)
PO	oral(ly)
POC	proof of concept
PPI	proton pump inhibitor
PR	partial response
PROTAC	PROteolysis Targeting Chimera
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
QD	every day
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
SAE	serious adverse event
sAI	steroidal aromatase inhibitor
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SERD	selective estrogen receptor downregulator
SmPC	summary of product characteristics
SoA	schedule of activities

Abbreviation	Term
SOC	standard of care
SOD	sum of the diameters
SRC	safety review committee
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
Tbili	total bilirubin
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
TRAE	treatment-related adverse event
TNM	tumor, node, metastasis
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	white blood cell

10.13. Appendix 13: 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 amendments can be found below:

[redacted] Amendment to Original Protocol (14 Dec 2022)

Overall Rationale for the Amendment: Updates made [redacted]

Section # and Name	Description of Key Changes	Brief Rationale	Substantial or Nonsubstantial
Appendix 12.1: [redacted] Requirements	Addition of Appendix 12.1: [redacted] Requirements • Addition of suggestion for bone mineral density testing due to anastrozole lowering circulating estrogen levels • Details added regarding co-administration of PPIs and H2 blockers. The concomitant use of PPIs with ARV-471 is not recommended. H2 blockers (eg, cimetidine, famotidine) or local antacids (eg, aluminum hydroxide, calcium carbonate, bismuth subsalicylate) may be used. Clarification that only participants for whom neoadjuvant endocrine monotherapy is deemed appropriate are eligible • Exclusion criteria now to exclude patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.	[redacted]	Nonsubstantial

10.14. Appendix 14: Signature Pages

10.14.1. Sponsor Approval Page

PROTOCOL TITLE: An Open-Label, Randomized, Non-Comparative Phase 2 Study of ARV-471 or Anastrozole in Post-Menopausal Women with ER+/HER2– Breast Cancer in the Neoadjuvant Setting

PROTOCOL NO: ARV-471-BC-201

VERSION: Global Amendment #1

I have read and approve of this protocol:

[redacted]

[redacted]
Date

10.14.2. Investigator Acknowledgment

PROTOCOL TITLE: An Open-Label, Randomized, Non-Comparative Phase 2 Study of ARV-471 or Anastrozole in Post-Menopausal Women with ER+/HER2– Breast Cancer in the Neoadjuvant Setting

PROTOCOL NO: ARV-471-BC-201

VERSION: Global Amendment #1

This protocol is a confidential communication of Arvinas Estrogen Receptor, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Arvinas Estrogen Receptor, Inc.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center:

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