

TITLE PAGE

Protocol Title	A Phase 1/2, open label, dose escalation, and cohort expansion clinical trial to evaluate the safety, tolerability, and pharmacokinetics of ARV-471 alone and in combination with palbociclib (IBRANCE®) in patients with estrogen receptor positive/human epidermal growth factor receptor 2 negative (ER+/HER2-) locally advanced or metastatic breast cancer, who have received prior hormonal therapy and chemotherapy in the locally advanced/metastatic setting
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Short Title	A Phase 1/2 open label, dose escalation, and cohort expansion clinical trial of ARV-471 alone and in combination with palbociclib (IBRANCE®) in patients with ER+/HER2- locally advanced or metastatic breast cancer
Study Phase	Phase 1/2
Sponsor Name	Arvinas Estrogen Receptor, Inc. (Arvinas)
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The following authorized representatives of Arvinas Estrogen Receptor, Inc. have approved this clinical research protocol “A Phase 1/2, open label, dose escalation, and cohort expansion clinical trial to evaluate the safety, tolerability, and pharmacokinetics of ARV-471 alone and in combination with palbociclib (IBRANCE®) in patients with estrogen receptor positive/human epidermal growth factor receptor 2 negative (ER+/HER2-) locally advanced or metastatic breast cancer, who have received prior hormonal therapy and chemotherapy in the locally advanced/metastatic setting”:

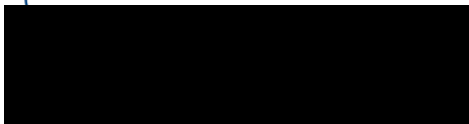
Signed by:   Signing Reason: I approve this document Signing Time: 19-Feb-2025 1:18:52 PM PST 	19-Feb-2025 _____ Date
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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

A Phase 1/2, open label, dose escalation, and cohort expansion clinical trial to evaluate the safety, tolerability, and pharmacokinetics of ARV-471 alone and in combination with palbociclib (IBRANCE®) in patients with estrogen receptor positive/human epidermal growth factor receptor 2 negative (ER+/HER2-) locally advanced or metastatic breast cancer, who have received prior hormonal therapy and chemotherapy in the locally advanced/metastatic setting.

Short Title

A Phase 1/2 open label, dose escalation, and cohort expansion clinical trial of ARV-471 alone and in combination with palbociclib (IBRANCE®) in patients with ER+/HER2- locally advanced or metastatic breast cancer.

Rationale

ARV-471 (PF-07850327) is a potent, selective, orally bioavailable PROteolysis-TArgeting Chimera (PROTAC®) small molecule that induces active degradation of the estrogen receptor (ER). ARV-471 is being developed for the treatment of patients with ER+/HER2- locally advanced or metastatic breast cancer (mBC). ARV-471 works by recruiting an E3 ligase to ubiquitinate ER which results in its subsequent degradation through the proteasome, a large, multi-subunit protein complex that degrades ubiquitinated proteins into small peptides. Such “active” degradation results in improved knockdown of tumor ER compared to fulvestrant in xenograft mouse models and produces tumor growth inhibition in vivo both as single agent and in combination with palbociclib. Unlike fulvestrant, which is administered via intramuscular (IM) injections, ARV-471 is administered as an oral tablet. Further, in early preclinical studies, ARV-471 has demonstrated greater ER degradation compared to other selective estrogen receptor downregulators (SERDs) in clinical development, such as AZD9496 and RAD1901 (Flanagan et al., 2017).

While fulvestrant has validated the importance of ER degradation as a therapeutic intervention in hormone receptor (HR)-positive mBC, up to 50% of the ER level can remain when compared to baseline levels following fulvestrant treatment for 6 months (Agrawal et al., 2016), providing an opportunity for a superior ER degrader such as ARV-471. Further, PROTAC degraders such as ARV-471 may provide advantage over small-molecule inhibitors, which can require high systemic exposure to achieve sufficient inhibition, often resulting in toxic side effects and eventual drug resistance.

Number of Study Centers

The study will include approximately 15 study centers.

Number of Patients

The study will include approximately 220 patients in total, including:

Part A – Phase 1 Dose Escalation: Approximately 100 patients are expected to be enrolled in the ARV-471 monotherapy dose-escalation (this number includes the potential to expand previously studied cohorts to a total of up to 20 patients per dose level).

Part B – Phase 2 Cohort Expansion: Approximately 60 patients will be enrolled in two ARV-471 monotherapy cohorts (each enrolling 30 patients).

Part C – Phase 1b Combination ARV-471 + palbociclib: Approximately 60 patients with ER+/HER2- advanced breast cancer will be enrolled, including approximately 6 to 12 evaluable patients in the dose escalation, approximately 20 evaluable patients each in Cohorts C3 and C4 in the expansion portion of this combination cohort, and up to 16 patients to obtain a minimum of 8 pharmacokinetic (PK) evaluable patients in Cohort C5. Additional patients may be enrolled in Cohort C5 at the discretion of the sponsor to replace patients who are not considered PK evaluable.

Overall Design

This study is designed as a 3-part, first-in-human, open label, sequential group study including a Phase 1/2, 3+3 dose escalation and cohort expansion of single agent ARV-471, and a Phase 1b investigation of ARV-471 in combination with palbociclib.

This study will assess the safety and tolerability and determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ARV-471, either as a single agent or in combination with palbociclib, in patients with locally advanced or mBC. The study will also assess clinical activity of ARV-471 at the RP2Ds for monotherapy and in combination with palbociclib. Additional evaluation will include single- and multiple-dose PK and biochemical activity.

Study Phase

Part A: Phase 1

Part B: Phase 2

Part C: Phase 1b

See [Figure 4](#) for the Overall Study Schema.

Part A – Phase 1 Dose Escalation: The Part A – Phase 1 Dose Escalation aims to determine the MTD and/or RP2Ds of ARV-471 as monotherapy. ARV-471 will be administered orally either once daily (QD) or twice daily (BID), and dose-escalation will follow a standard 3+3 design (as described below under “Dose Escalation”). The first cohort will be Cohort 1 and subsequent cohorts will be Cohort 2, Cohort 3, etc.

Additional patients (up to 20 total per dose level) may be added to previously studied dose-escalation cohorts once the Cohort Review Committee (CRC) has deemed the dose to be safe.

These additional patients will allow for further characterization of the safety of ARV-471 as well as its PK/pharmacodynamic (PD) profile.

The CRC will recommend, and the Arvinas' Chief Medical Officer (CMO) will approve, the dose(s) including RP2Ds and schedules selected for use in the Part B – Phase 2 Cohort Expansion.

Part B – Phase 2 Cohort Expansion: Part B aims to assess the activity of the recommended doses of ARV-471 monotherapy in a population of patients who have previously received a CDK4/6 inhibitor and experienced progression on endocrine therapy in the advanced/metastatic setting, but have received no more than 1 prior chemotherapy regimen. In Cohort B1, approximately 30 patients will receive ARV-471 as monotherapy at 200 mg QD. In Cohort B2, approximately 30 patients will receive ARV-471 as monotherapy at 500 mg QD. If both cohorts are open to accrual simultaneously, sequential patients may be enrolled to each cohort in an alternating fashion.

A Safety Review Committee (SRC) will be formed prior to the enrollment of the first patient in Part B. The SRC will be composed of Sponsor's personnel responsible for the execution and safety oversight of this clinical trial, as well as selected Principal Investigators. The SRC will be responsible for monitoring the ongoing safety data of patients enrolled in the cohort expansion part on a quarterly basis beginning with the enrollment of the first patient in Part B and ending when all patients have completed study drug treatment or final database lock occurs.

Part C – Combination ARV-471 + palbociclib: Part C aims to determine the safety and recommended dose of ARV-471 in combination with palbociclib. ARV-471 will be administered orally QD, and palbociclib will be administered according to the approved palbociclib (IBRANCE®) United States Prescribing Information (USPI) ([Pfizer Inc., 2019](#)).

Part C will include two dose-escalation levels for ARV-471 in combination with palbociclib prior to the expansion cohorts: 1) 200 mg QD (Cohort C1; initially 180 mg QD but rounded up to 200 mg QD upon availability of the 100-mg tablets), and 2) 400 mg QD (Cohort C2). The CRC will review the safety data of each cohort and recommend escalation or not. If Cohorts C1 and C2 are approved for escalation, expansion at the dose of 500 mg QD ARV-471 with palbociclib (Cohort C3) and 200 mg QD ARV-471 with palbociclib (Cohort C4) will begin. If an intermediate dose for combination is recommended by the CRC based on the two dose-escalation Cohorts C1 and C2, then the expansion cohort C3 will use that recommended dose in combination with palbociclib. Cohorts C1 and C2 will consist of 3-6 patients each, followed by approximately 20 patients each enrolled in Cohorts C3 and C4. If Cohorts C3 and C4 are open to accrual simultaneously, sequential patients may be enrolled to each cohort in an alternating fashion.

Part C will include Cohort C5, which aims to evaluate the safety of treatment with palbociclib 100 mg QD (21 days on followed by 7 days off treatment) and ARV-471 200 mg QD and to further evaluate the steady state PK of palbociclib in the absence and presence of ARV-471 200 mg. In Cycle 1, palbociclib 100 mg will be given alone for 8 days (Cycle 1 Day 1 [C1D1])

through Cycle 1 Day 8 [C1D8]) prior to starting ARV-471 200 mg QD on Cycle 1 Day 9. Palbociclib 100 mg QD will begin on C1D1 and be given for 21 days followed by 7 days off treatment (Figure 1). In Cycles 2 and beyond, patients will receive, starting on Day 1, ARV-471 200 mg QD continuously and palbociclib 100 mg QD for 21 days followed by 7 days off treatment. Cohort C5 will enroll up to 16 patients to obtain a minimum of 8 PK evaluable patients.

The SRC will continue to monitor safety throughout Part C for patients receiving ARV-471 in combination with palbociclib until all patients have completed study drug treatment or final database lock occurs.

Objectives and Endpoints

The objectives and endpoints are presented below.

Part A – Phase 1 Dose Escalation	
Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of ARV-471 in successive cohorts of patients in order to estimate the maximum tolerated dose and select the RP2Ds	The following safety endpoints will be assessed: • First cycle dose-limiting toxicities • Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
Secondary	
To characterize the single dose and steady-state PK of ARV-471 and ARV-473	The following PK parameters will be assessed when applicable after a single dose and after multiple doses: AUC_{0-tau}, AUC_{0-last}, C_{max}, C_{min}, CL/F, T_{max}, Vd/F, and accumulation ratios, Effective T_{1/2}, MRC_{max}, and MRAUC_{0-tau}
To explore preliminary anti-tumor activity	Anti-tumor activity of ARV-471 will be assessed by evaluating the following: • Overall response rate (ORR) per RECIST 1.1 • Clinical benefit rate (CBR) based on the summation of complete responses (CRs), partial responses (PRs) and stable disease (SD) of 24 weeks duration or longer • Disease control rate (DCR; CR, PR, SD) • Time to event endpoints: progression-free survival (PFS), duration of response (DOR)

Part A – Phase 1 Dose Escalation	
Objectives	Endpoints
Exploratory	
To characterize baseline ESR1 mutational status, which is a potential mechanism of resistance to prior ER-targeted therapies, and relevant molecularly defined subsets of patients	ESR1 mutational status in ctDNA and/or tumor tissue
To assess PD effects of ARV-471 on exploratory biomarkers	ER, progesterone receptor, and Ki-67 protein levels in pre- and post-treatment tumor biopsies in patients with accessible tumor tissue

Abbreviations: AUC_{0-last}=area under the plasma concentration-time curve from time zero to time of last measurable concentration; AUC_{0-tau}=area under the plasma concentration-time curve during a dosing interval, calculated by linear up/log down trapezoidal summation; CL/F=apparent oral plasma clearance; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; CR, complete response; ctDNA=circulating tumor deoxyribonucleic acid; DOR, duration of response; Effective T_{1/2}=Effective half-life based on accumulation ratio; ER=estrogen receptor; ESR1=estrogen receptor 1; MRAUC_{0-tau}=ARV-473 to ARV-471 ratio for AUC_{0-tau}; MRC_{max}=ARV-473 to ARV-471 ratio for C_{max}; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PK=pharmacokinetics; PD=pharmacodynamic; PR, partial response; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; RP2D, recommended Phase 2 dose; T_{max}=time to C_{max}; Vd/F=apparent volume of distribution after non-intravenous administration.

Note: ORR, CBR, DCR, DOR, and PFS will be evaluated using RECIST 1.1.

Part B – Phase 2 Cohort Expansion	
Objectives	Endpoints
Primary	
To evaluate the anti-tumor activity of ARV-471 in patients with locally advanced or mBC	The anti-tumor activity of ARV-471 will be assessed by evaluating the following: • CBR based on the summation of CRs, PRs and stable disease of 24 weeks duration or longer
Secondary	
To further evaluate the anti-tumor activity of ARV-471 in patients with locally advanced or mBC	Anti-tumor activity of ARV-471 will be assessed by evaluating the following: • ORR per RECIST 1.1 in patients with measurable disease at baseline • DOR • PFS • OS

Part B – Phase 2 Cohort Expansion	
Objectives	Endpoints
To further evaluate the safety and tolerability of ARV-471 in patients with locally advanced or mBC	- Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug - Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
To determine plasma concentrations of ARV-471 and ARV-473	Pre-dose concentrations of ARV-471 and ARV-473
Exploratory	
To characterize baseline ESR1 mutational status, which is a potential mechanism of resistance to prior ER-targeted therapies, and relevant molecularly defined subsets of patients	ESR1 mutational status in ctDNA and/or tumor tissue
To assess PD biomarkers of ARV-471	ER, progesterone receptor, and Ki-67 protein levels in pre- and post-treatment tumor biopsies in patients with accessible tumor tissue

Abbreviations: CR=complete response; ctDNA=circulating tumor deoxyribonucleic acid; ER=estrogen receptor; ESR1=estrogen receptor 1; mBC=metastatic breast cancer; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PK=pharmacokinetics; PD=pharmacodynamic; PR=partial response; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1.

Note: CBR, ORR, DOR, and PFS will be evaluated using RECIST 1.1.

Part C – Combination ARV-471 + Palbociclib	
Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of ARV-471 in combination with palbociclib and select the recommended dose/schedule for the combination	The following safety endpoints will be assessed: - First cycle dose-limiting toxicities, determination of a MTD, if applicable, among the doses evaluated - Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug combination - Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing

Part C – Combination ARV-471 + Palbociclib	
Objectives	Endpoints
Secondary	
To characterize the first dose and steady-state PK of ARV-471, ARV-473, and palbociclib when ARV-471 is administered in combination with palbociclib	The following PK parameters will be assessed for ARV-471, ARV-473, and palbociclib when applicable after a single dose and after multiple doses: AUC _{0-tau} , AUC _{0-last} , C _{max} , C _{min} , CL/F, T _{max} , Vd/F, and accumulation ratios, Effective T _{1/2} , MRC _{max} , and MRAUC _{0-tau}
To characterize the steady state PK of palbociclib when given alone and in combination with ARV-471 in Part C Cohort C5.	PK parameters of palbociclib AUC _{0-tau} , and C _{max} , and other PK parameters if data permits (T _{max} , CL/F, Vd/F, etc)
To assess preliminary anti-tumor activity of ARV-471 in combination with palbociclib	Anti-tumor activity of ARV-471 in combination with palbociclib will be assessed by evaluating the following: • ORR per RECIST 1.1 in patients with measurable disease at baseline • CBR based on the summation of CRs, PRs, and stable disease of 24 weeks duration or longer • Time to event endpoints: PFS, DOR, OS
Exploratory	
To characterize tumor mutational status, including ESR1, which is a potential mechanism of resistance to prior ER-targeted therapies	Determine the mutational status of ESR1 and other genes related to ER signaling in ctDNA and/or tumor tissue
To assess PD effects of ARV-471 on exploratory biomarkers	ER, progesterone receptor, and Ki-67 protein levels in pre- and post-treatment tumor biopsies in patients with accessible tumor tissue

Abbreviations: AUC_{0-last}=area under the plasma concentration-time curve from time zero to time of last measurable concentration; AUC_{0-tau}=area under the plasma concentration-time curve during a dosing interval, calculated by linear up/log down trapezoidal summation; CL/F=apparent oral plasma clearance; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; ctDNA=circulating tumor deoxyribonucleic acid; ER=estrogen receptor; ESR1=estrogen receptor 1; MRAUC_{0-tau}=ARV-473 to ARV-471 ratio for AUC_{0-tau}; MRC_{max}=ARV-473 to ARV-471 ratio for C_{max}; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PK=pharmacokinetics; PD=pharmacodynamic; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; T_{max}=time to C_{max}; Vd/F=apparent volume of distribution after non-intravenous administration.

Note: ORR, CBR, DOR, and PFS will be evaluated using RECIST 1.1.

Inclusion Criteria

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

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C – Phase 1b Combination
1.	Patients at least 18 years of age at the time of signing the informed consent.	Same	Same
2.	Patients must have histologically or cytologically confirmed ER+ and HER2- advanced breast cancer. Advanced breast cancer is metastatic, recurrent, or locally advanced unresectable breast cancer for which standard curative therapy is no longer effective or does not exist. a. ER+ disease must be documented by IHC per ASCO/CAP Guidelines (Hammond et al., 2010). b. HER2- disease must be documented by either IHC or in-situ hybridization per ASCO/CAP guidelines (Wolff et al., 2018).	Same	Same
3	Patients must have measurable or nonmeasurable disease by RECIST 1.1, with radiologic tumor assessments performed within 28 days of the first dose of therapy.	Same	Same
4	Women must be postmenopausal due to surgical or natural menopause, which requires at least 1 of the following: (a) prior bilateral oophorectomy, (b) age ≥ 60 years, (c) age < 60 years and amenorrhoeic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol levels in the postmenopausal range; or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin. Patients on ovarian suppression therapy should remain on such therapy in the absence of intolerable symptoms.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C – Phase 1b Combination
5	Men must agree to use contraception as detailed in Appendix 6 of this protocol during the treatment period and for 6 months after the last dose of study treatment and refrain from donating sperm during this period.	Same	Same
6.	Patients must have received: - at least 2 prior endocrine regimens in any setting (neoadjuvant, adjuvant or advanced/metastatic) - a CDK4/6 inhibitor - up to 3 prior regimens of cytotoxic chemotherapy in the locally advanced or metastatic setting All such therapy must be discontinued at least 14 days prior to enrollment.	Patients must have received: - at least 1 prior endocrine regimen for a minimum of 6 months in the locally advanced or metastatic setting; if more than 1 prior endocrine regimen has been administered, only one of the regimens must have been administered for a minimum of 6 months in the locally advanced or metastatic setting - a CDK4/6 inhibitor - up to 1 prior regimen of cytotoxic chemotherapy in the locally advanced or metastatic setting The patient must have had evidence of disease progression on their last endocrine based therapy. All such therapy must be discontinued at least 14 days prior to enrollment.	Patients must have received: - At least 1 prior endocrine regimen - No more than 2 prior chemotherapy regimens for advanced disease. All such therapy must be discontinued at least 14 days prior to enrollment.

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C – Phase 1b Combination
7	Patients must be willing to undergo a core biopsy of accessible tumor within 4 weeks prior to the initiation of study treatment and a follow-up biopsy on-treatment for ER IHC testing and PD studies. (Patients without accessible tumor tissue may be eligible after discussion with the Medical Monitor).	Same	Same
8	Patients must have 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): a. ANC of $\geq 1500/\text{mm}^3$ or $\geq 1.5 \times 10^9/\text{L}$. b. Platelets of $\geq 100,000/\text{mm}^3$ or $\geq 100 \times 10^9/\text{L}$. c. Hemoglobin ≥ 9 g/dL.	Same	Same
9	aPTT $\leq 1.25 \times \text{ULN}$ and INR ≤ 1.25 .	aPTT $\leq 1.25 \times \text{ULN}$ and INR ≤ 1.25 unless the patient is receiving anticoagulation, then aPTT and INR should be within the therapeutic range of the intended use.	aPTT $\leq 1.25 \times \text{ULN}$ and INR ≤ 1.25 unless the patient is receiving anticoagulation, then aPTT and INR should be within the therapeutic range of the intended use.
10	Patients must have adequate renal function defined as serum creatinine of $\leq 1.5 \times \text{ULN}$ or an estimated creatinine clearance of ≥ 50 mL/min by Cockcroft Gault.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C – Phase 1b Combination
11	Patients must have adequate liver function defined as: a. Total serum bilirubin of $\leq 1.5 \times$ ULN unless the patient has documented Gilbert syndrome. b. AST and ALT of $\leq 2.5 \times$ ULN if there is <u>NO</u> liver involvement secondary to tumor OR $\leq 5.0 \times$ ULN if there is liver involvement secondary to tumor.	Same	Same
12	Any toxicity from prior anti-cancer therapy other than alopecia must have resolved to baseline severity or Grade ≤ 1 NCI CTCAE version 5.0	Same	Same
13	Patients must agree and be capable of taking oral medication without crushing, dissolving, or chewing tablets/capsules.	Same	Same
14	Patients must have an ECOG Performance Status of 0 or 1	Same	Same
15	Patients must be willing and capable of giving signed informed consent and comply with the requirements and restrictions listed in the ICF and in the protocol.	Same	Same

Abbreviations: aPTT=activated partial thromboplastin time; ANC=absolute neutrophil count; ALT=alanine aminotransferase; ASCO=American Society of Clinical Oncology; AST=aspartate aminotransferase; CAP=College of American Pathologists; CDK=cyclin-dependent kinase; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; FSH=follicle-stimulating hormone; HER2=human epidermal growth factor 2; ICF=informed consent form; IHC=immunohistochemistry; INR=international normalized ratio; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PD=pharmacodynamic; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; ULN=upper limit of normal.

Exclusion Criteria

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

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
1	Patients with known symptomatic brain metastases requiring steroids (above physiologic replacement doses). Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to first dose of study drug, have discontinued high dose corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable as judged by the Investigator.	Same	Same
2	Patients who have received ≥ 4 regimens of chemotherapy for locally advanced or mBC	Patients who have received >1 regimen of chemotherapy for locally advanced or mBC	Patients who have received >2 regimens of chemotherapy for advanced/metastatic disease (regardless of prior adjuvant chemotherapy use) in addition to endocrine therapy
3	Receipt of prior anti-cancer or other investigational therapy within 14 days prior to the first administration of study drug. For prior therapies with a half-life longer than 3 days, the interval must equal 28 days prior to the first administration of study drug and the patient must have documented disease progression.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
4	Patients who have initiated therapy with bone-modifying agents (bisphosphonates, denosumab, or similar) within 14 days of enrollment. (Patients who are receiving bone-modifying agents are eligible for this study provided the bone-modifying agent was started more than 14 days prior to study enrollment.)	Same	Same
5	Patients with active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus, hepatitis C virus, known HIV, or AIDS-related illness. In equivocal cases, patients whose viral load is negative may be eligible. HIV seropositive patients who are healthy and low risk for AIDS-related outcomes could be considered eligible. Eligibility criteria for HIV positive patients should be evaluated and discussed with the Medical Monitor and will be based on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions (eg, opportunistic infections), and status of HIV treatment.	Same	Same
6	Major surgery (as defined by the Investigator) within 4 weeks of first dose of study drug.	Same	Same
7	Radiation therapy within 4 weeks of first dose of study drug or prior irradiation to >25% of the bone marrow. Palliative radiation for the alleviation of pain due to bone metastasis will be allowed during the study.	Same	Same
8	Previous high-dose chemotherapy requiring stem cell rescue.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
9	Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen in this study. Patients with a prior or concurrent malignancy whose natural history or treatment that does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen in this study may be eligible but must be discussed with the Medical Monitor.	Same	Same
10	Prior treatment with ARV-471.	Same	Same
11	Any of the following in the previous 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease.	Same	Same
12	Any of the following in the previous 6 months: congenital long QT syndrome, Torsade de Pointes, arrhythmias (including 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). If a patient has a cardiac rhythm device/pacemaker placed and QTcF ≤ 470 msec, the patient can be considered eligible. Patients with cardiac rhythm device/pacemaker must be discussed in detail with the Medical Monitor to judge eligibility.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
13	History of symptomatic cardiac valve disease. Patients with mitral valve prolapse which is asymptomatic or not associated with clinically significant sequelae (eg, mitral regurgitation) are eligible. Any case of mitral valve prolapse must be discussed with the Medical Monitor prior to enrollment to confirm eligibility.	Same	Same
14	Other acute or chronic severe medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.	Same	Same
15	Active inflammatory gastrointestinal disease, chronic diarrhea, or previous gastric resection or lap band surgery. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed unless it meets a criterion under Exclusion Criterion #17.	Same	Same
16	Patients who fall into any of the following: a. Investigational site staff members directly involved in the conduct of the study and their family members; OR b. Site staff members otherwise supervised by the Investigator; OR c. Patients employed by the Sponsor who are directly involved in the conduct of the study.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
17	Concurrent administration of medications or foods that are strong inhibitors and inducers of cytochrome P450 3A4, sensitive substrates of CYP2B6 or those with narrow therapeutic indices, sensitive P-gp substrates or those with narrow therapeutic indices, and any medications that are known to prolong the QT interval (see Appendix 9). Prior use must be discontinued 2 weeks (1 week for medications that are known to prolong the QT interval) before the start of study drug treatment.	Same	Same
18	n/a	n/a	Discontinuation or dose reduction of prior palbociclib due to: • Interstitial lung disease • Grade 3 or 4 toxicity (patients previously dose reduced for toxicity may be considered eligible with approval by Medical Monitor) • Hypersensitivity
19	QTcF > 470 msec	Same	Same

Abbreviations: AIDS=acquired immunodeficiency syndrome; AR=androgen receptor; AST=aspartate aminotransferase; CD=cluster of differentiation; GI=gastrointestinal; HIV=human immunodeficiency virus; mBC=metastatic breast cancer; n/a=not applicable; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; P-gp=P-glycoprotein; QTcF=corrected QT interval by Fridericia's method.

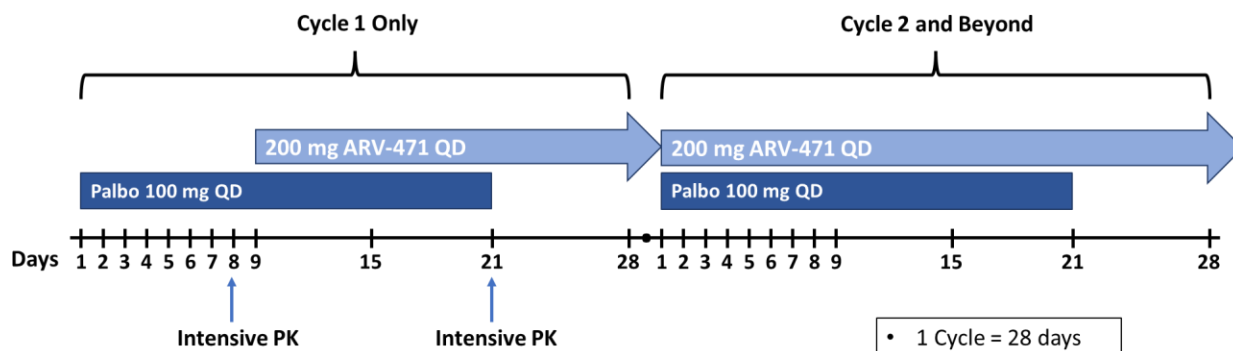
Treatment Groups and Duration

ARV-471 will be administered orally with food (eg, light meal of approximately 400 to 600 calories which includes a mixture of fat, carbohydrates, and protein), in continuous dosing over 28-day cycles. The ARV-471 dose and schedule are specific for each study part/cohort, as described under Study Design ([Section 4](#)) and Dose Escalation ([Section 4.4.1](#)). Upon availability of the 100-mg tablet, the total daily dose for each patient is adjusted/rounded to account for the available tablet strength (ie, patients receiving 180 mg QD begin receiving a rounded dose of 200 mg QD, while patients receiving 360 mg QD begin receiving a rounded dose of 400 mg QD). In addition, as PK analyses suggest similar exposure resulting from the QD and BID dosing (see [Section 4.3.4](#)), patients on a BID schedule are transitioned to receive the same total daily dose on a QD schedule utilizing the 100-mg tablets.

Patients in Cohorts C1-C4 of Part C will also receive palbociclib according to the recommended starting dose and regimen (125 mg QD for 21 days followed by 7 days off-treatment) as per the approved palbociclib (IBRANCE®) USPI. In these cohorts, palbociclib 125 mg will be administered at the same time as ARV-471. During the dose-escalation portion of Part C, patients must start at the standard full dose of palbociclib. Once a recommended dose of ARV-471 in combination with palbociclib has been determined, patients previously treated with palbociclib at a reduced dose may be allowed to enroll at a lower palbociclib dose in consultation with the Arvinas Medical Monitor (see Exclusion Criterion #18).

In Cohort C5, palbociclib 100 mg QD will begin on C1D1 and be given for 21 days followed by 7 days off treatment ([Figure 1](#)). In Cycle 1, palbociclib 100 mg will be given alone for 8 days (C1D1 through C1D8), prior to starting ARV-471 200 mg QD on Cycle 1 Day 9. In Cycles 2 and beyond, patients will receive, starting on day 1, ARV-471 200 mg QD continuously and palbociclib 100 mg QD for 21 days followed by 7 days off-treatment.

A patient may continue treatment at the discretion of the Principal Investigator until a treatment discontinuation criterion is met (see [Section 7.1](#)). Patients who have evidence of radiographic disease progression may be considered for continued study therapy provided the Principal Investigator has determined that they are still benefiting from study therapy. All such requests must be reviewed and approved by the Sponsor's Medical Monitor.

Figure 1 Part C Cohort C5: ARV-471 and Palbociclib Treatment Regimen

Abbreviations: Palbo=palbociclib, PK=pharmacokinetics, QD=once daily.

Dose Escalation

Part A – Phase 1 Dose Escalation: The Part A dose-escalation will be conducted according to a 3+3 design (Figure 2). The Part A – Phase 1 Dose Escalation will be based on the CRC’s review of all safety data from the patients enrolled into the cohort under review. Dose-limiting toxicities (DLTs) (see Appendix 5 for DLT definition) will be evaluated during the first (28-day) cycle. Patients in Cycle 1 who for any reason other than toxicity did not receive at least 80% of their intended regimen (22 doses of 28 planned for 80% of ARV-471) will be replaced. In addition, PK data from the cohort under review may be considered, as appropriate.

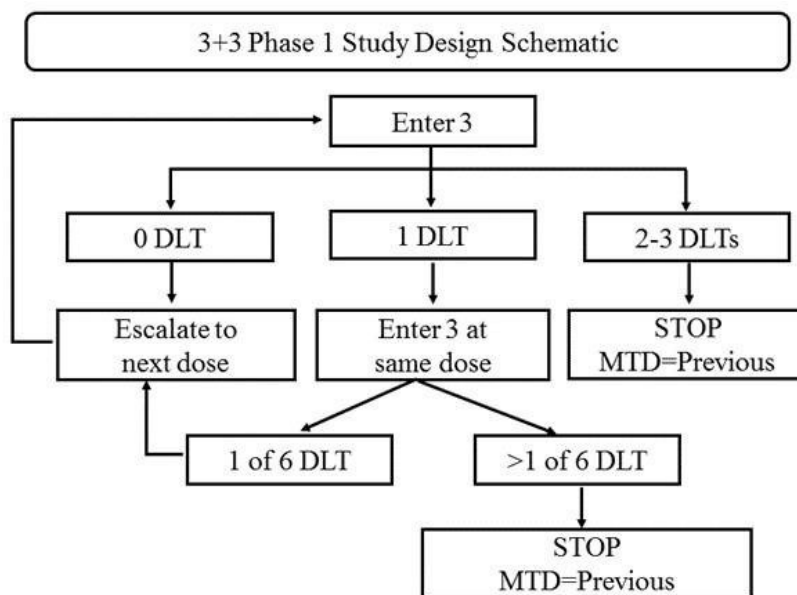
Initially, 3 patients will be treated at each dose level. If a DLT is observed in 1 of the 3 initial patients treated, 3 additional patients will be enrolled and treated at the same dose level (these will not be considered backfill patients). If no further DLT is observed, the next dose level may be open after review and approval by the CRC. If a second DLT is observed, the dose level will be considered to have exceeded the MTD, dose escalation will stop, and the dose will be reduced to the next lower dose level deemed safe by the CRC. An intermediate dose level may be explored, if deemed appropriate by the CRC.

At the discretion of the Principal Investigator, optional intra-patient dose escalation is permitted if the next higher dose level has been declared safe by the CRC and if the patient has had no Grade 2 or greater toxicities deemed related to study drug. Permission by the Arvinas’ Medical Monitor is also required.

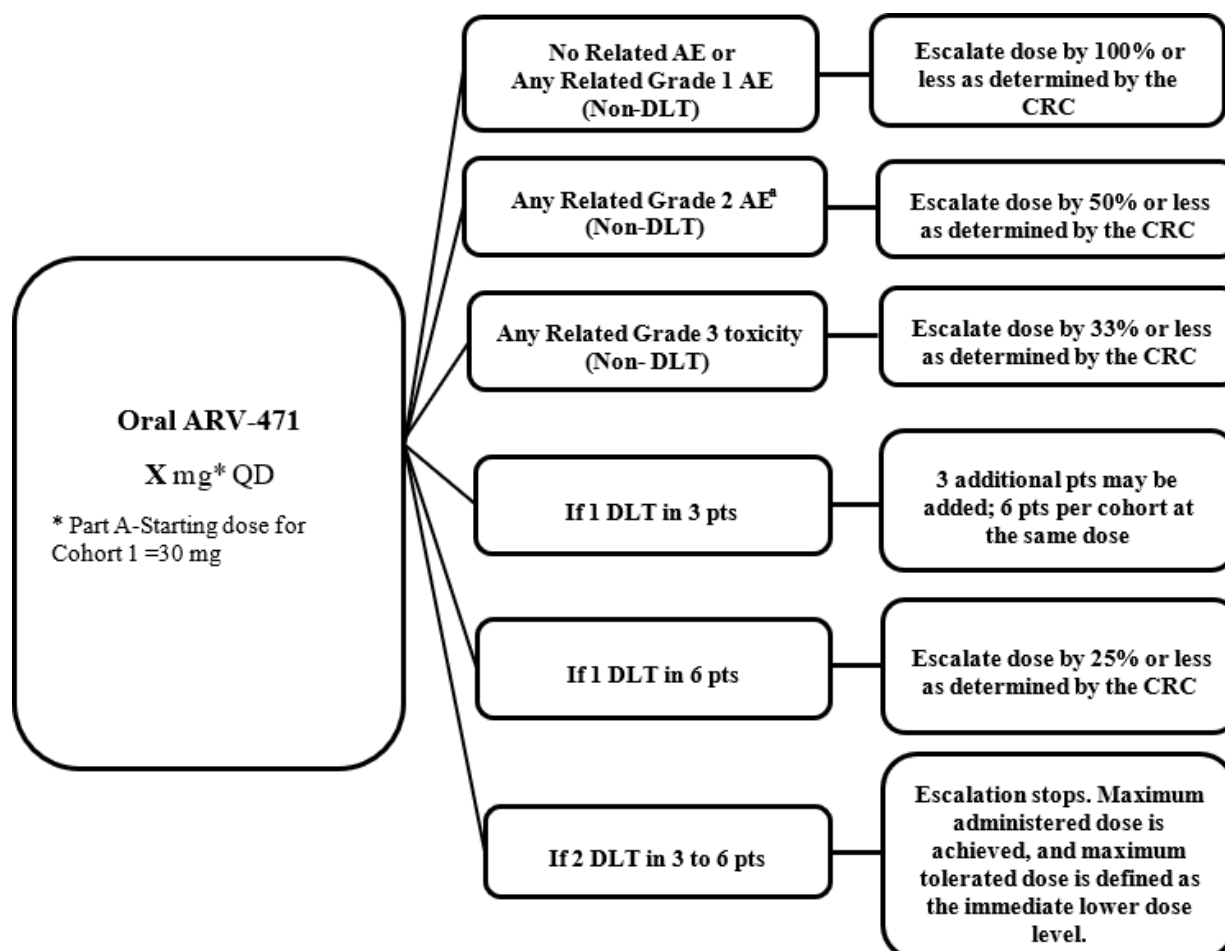
The dose escalation schema for Part A is presented below (Figure 3). The initial starting dose for dose-escalation was 30 mg QD. As of 13 April 2021, the dose escalation has proceeded through 30 mg QD, 60 mg QD, 120 mg QD, 180 mg QD, 360 mg QD, 500 mg QD total daily dose (administered initially as a 250-mg BID dose, transitioned to QD dosing upon availability of 100-mg tablets), and 700-mg total daily dose level (administered initially as 400/300 BID dosing, transitioned to QD dosing upon availability of 100-mg tablets). Dose-escalation is

planned to continue until identification of an MTD or until other factors suggest dose escalation should be halted prior to identification of an MTD (eg, long term tolerability, pharmacodynamic findings, plateauing of absorption), with consideration to the following:

- No DLTs have been reported with ARV-471 monotherapy among the 45 patients treated in dose escalation and cohort expansion at doses up to 250 mg BID (500 mg total daily dose; N=6). In addition, 2 patients have received the 700-mg total daily dose for more than 28 days with no DLT.
- The majority of treatment-related adverse events (AEs) are Grade 1 in severity, with treatment-related AEs in $\geq 10\%$ of patients limited to nausea, fatigue and arthralgia.
- Except for one patient in the 360-mg cohort who discontinued study treatment due to a Grade 3 thromboembolic event that was assessed as possibly related to treatment, there have been no additional Grade 3 treatment-related AEs or treatment discontinuation due to toxicity.
- Dose-related increase in PK is through 500-mg dose level.
- The no observed adverse effect level (NOAEL) in nonclinical toxicology studies (female rat) was 100 mg/kg/day, which is equivalent to a human dose of approximately 960 mg. Refer to the Investigator's Brochure for details.
- ARV-471 efficacy in patient-derived xenograft models was dose-related.

Figure 2 Part A – Phase 1 Dose Escalation: 3+3 Schema

Abbreviations: DLT=dose-limiting toxicity; MTD=maximum tolerated dose.

Figure 3 Part A Dose Escalation Schema

Abbreviations: AE=adverse event; CRC=Cohort Review Committee; DLT=dose-limiting toxicity; MTD=maximum tolerated dose; N=number of patients; PD=pharmacodynamic; PK=pharmacokinetic; pts=patients; QD=once daily; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; RP2D=recommended Phase 2 dose.

NOTE: The dose is rounded to the nearest multiple of 50 or 100 to accommodate available dosage strength(s). a. Except for AEs judged by the CRC not to represent any safety risk to the patient.

Part C: The Part C dose-escalation levels for ARV-471 in combination with palbociclib are 200 mg QD (Cohort C1; initially 180 mg QD but rounded up to 200 mg QD upon availability of the 100-mg tablets) and 400 mg QD (Cohort C2), and the expansion cohorts will be 500 mg QD (Cohort C3) and 200 mg QD (Cohort C4). The CRC will review all safety and PK data from the patients enrolled in the dose escalation cohorts and endorse dose escalation. Hematologic AEs will be considered related to palbociclib and will be managed according to the current palbociclib (IBRANCE®) USPI.

DLTs (see [Appendix 5](#) for DLT definition) will be evaluated during the first (28-day) cycle. Patients in Cycle 1, who for any reason other than ARV-471 toxicity, do not receive at least 70%

of each agent (eg, 15 doses of 21 planned for palbociclib irrespective of dose; 20 doses of 28 planned for 70% of ARV-471) will be replaced.

Initially, up to 3 patients will be treated in Cohort C1 at 200 mg QD of ARV-471 (or 180 mg QD if prior to availability of the 100-mg tablets) in combination with the recommended dose of palbociclib as per the current palbociclib (IBRANCE®) USPI. If a DLT, as defined specifically for Part C (see [Appendix 5](#)), is observed in 1 of the 3 initial patients treated, 3 additional patients will be enrolled and treated at the same dose level. Alternatively, if no DLT is observed in the initial 3 patients but there are related Grade 2 or 3 non-hematologic AEs of clinical significance as determined by the CRC, 3 additional patients may also be treated at the same dose level. If there are no DLTs, or if there is 1 DLT out of 6 patients then the CRC will review and approve escalation to Cohort C2, at the 400-mg QD dose with palbociclib. The same review process will be followed for approval to begin Cohort C3, in which approximately 20 patients will receive ARV-471 at 500 mg QD with palbociclib. In expansion Cohort C4, approximately 20 patients will receive ARV-471 at 200 mg QD with palbociclib.

An intermediate dose level below 500 mg QD may be recommended by the CRC for expansion Cohort C3. If a second DLT is observed in any given dose-escalation cohort, the dose level will be considered to have exceeded the MTD, dose escalation will stop, and the dose will be reduced to the next lower dose level deemed safe by the CRC or an intermediate dose may be tested. The dose of ARV-471 that is administered in combination with palbociclib will not exceed the highest dose cleared in Part A. Approximately 40 patients (approximately 20 each in Cohorts C3 and C4) are expected to receive ARV-471 in combination with palbociclib after the dose-escalation phase of the combination cohort and those patients will be monitored by the SRC.

Dose Interruption and Modification

See [Section 4.4.2](#) for details.

Statistical Methods

A Statistical Analysis Plan (SAP) will be written to detail the analysis of all clinical, efficacy, safety, and laboratory data collected for the study. The SAP will contain analyses of data from the Part A – Phase 1 Dose Escalation, Part B – Phase 2 Cohort Expansion, and Part C – Phase 1b combination.

Sample size calculations:

- Part A – Phase 1 Dose Escalation: It is anticipated that 4 to 8 dose-escalation levels may be required to determine the MTD, and that at least one cohort will be expanded up to a total of 20 patients to allow for further characterization of the safety of ARV-471 as well as its PK/pharmacodynamic profile. Therefore, approximately 100 patients will be enrolled in Part A of this study.

- Part B – Phase 2 Cohort Expansion: Approximately 60 patients will be enrolled in 2 ARV-471 monotherapy cohorts (each enrolling 30 patients). A sample size of approximately 60 patients for the efficacy analysis set will provide estimation of the CBR with 95% confidence interval (CI) width 24.4% (or 34.7% for each cohort), if the ORR is 30% (ie, the 95% CI based on Clopper-Pearson method for the CBR will be estimated as 18.8%, 43.2%).
- Part C – Phase 1b Combination ARV-471 + Palbociclib: It is anticipated that approximately 6-12 evaluable patients will be enrolled in a dose escalation, approximately 40 evaluable patients (approximately 20 each in Cohorts C3 and C4) will be treated in an expansion phase, and up to 16 patients will be treated in Cohort C5 to obtain a minimum of 8 PK evaluable patients to allow for further characterization of the safety and PK/pharmacodynamic profile of the combination. Therefore, approximately 60 patients will be enrolled in Part C of this study.

Statistical Analyses: Descriptive statistics will be used to display the data and results from each study part. Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a category. AEs and serious adverse events (SAEs) will be tabulated by system organ class and preferred term. Laboratory test results after the first dose of ARV-471 will be summarized by shift from baseline value and CTCAE grade. Time to event endpoints such as DOR, PFS and overall survival (OS) will be plotted and estimated using the Kaplan-Meier method. Binary efficacy endpoints such as ORR, CBR, and DCR, and their 2sided 95% CIs, will be calculated using the Clopper-Pearson method.

Safety Monitoring

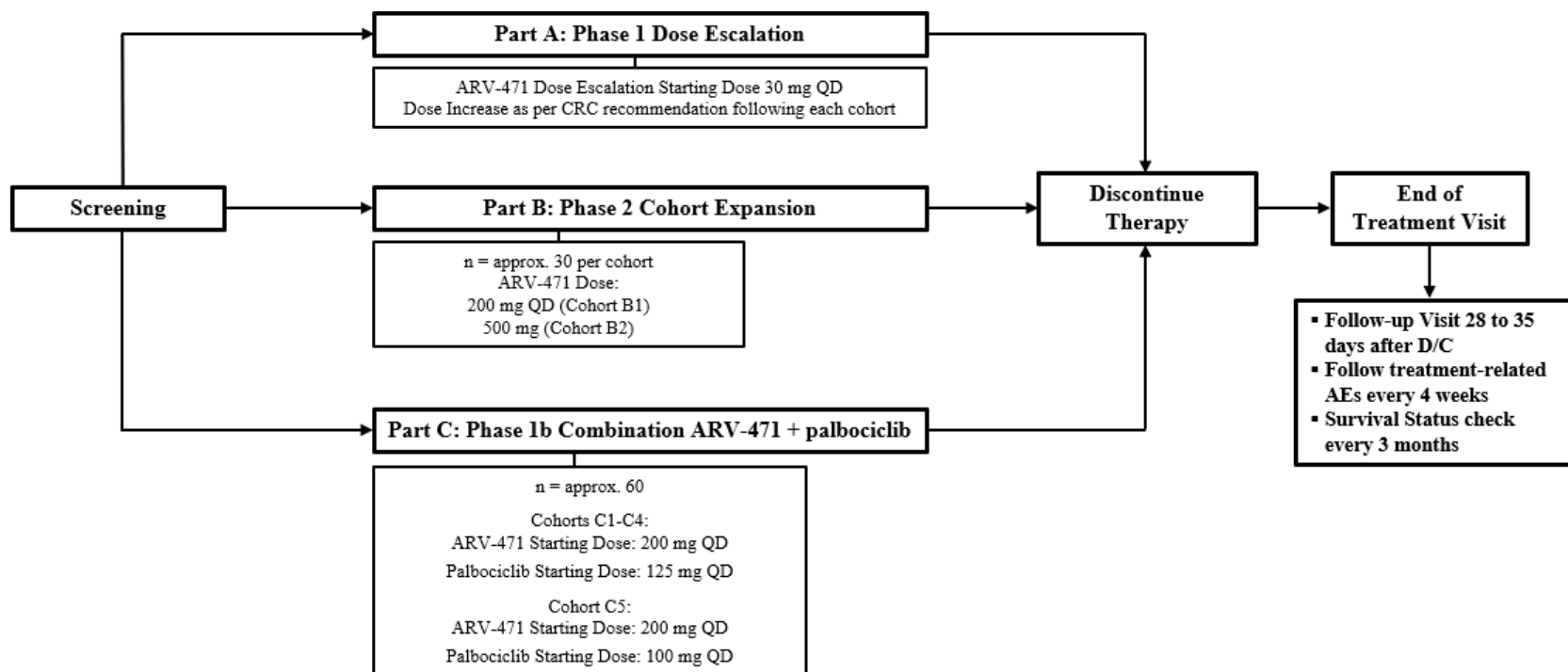
Part A – Phase 1 Dose Escalation: The CRC will be established to review safety and PK data (as appropriate) from patients enrolled into the Phase 1 Dose Escalation. The CRC membership, at a minimum, will be composed of the Principal Investigators/Sub-Investigator designees from each clinical trial site (one of whom is considered to be a specialist with expertise in oncology), a Sponsor representative(s), a pharmacovigilance representative, and a statistician. Additional members may be added to the CRC as appropriate. The CRC is responsible for reviewing and evaluating unblinded safety data after each cohort has completed 28 days of treatment (Cycle 1) and subsequently at regularly scheduled meetings as outlined in the cohort review meeting guidelines. The CRC 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 CRC will also be responsible for the initiation of enrollment to the next dose level and determination of the dose to be tested at each of the next dose levels. The CRC will recommend and the Sponsor's CMO will approve, the RP2D selected for Part B, from one or more doses and/or schedules evaluated from the Part A – Phase 1 Dose Escalation.

Part B – Phase 2 Cohort Expansion: The Safety Review Committee (SRC) will be established to review the safety and PK data from patients enrolled into the Part B – Phase 2 Cohort Expansion. The SRC will be formed prior to the enrollment of the first patient in the Part B – Phase 2 Cohort Expansion. The SRC will be composed of Sponsor’s personnel responsible for the execution and safety oversight of this clinical trial as well as selected Principal Investigators. The SRC will be responsible for monitoring the ongoing safety data of patients enrolled in the cohort expansion on a quarterly basis beginning with the enrollment of the first patient in Part B and ending when all patients have completed study drug treatment or final database lock occurs. Additional details will be provided in the SRC guidelines.

Part C – Phase 1b combination: The CRC established in Part A will comprise the committee for Part C. They will review safety and PK data (as appropriate) from patients enrolled into the Phase 1b Dose Escalation. The CRC membership, at a minimum, will be composed of at least 4 Principal Investigators/Sub-Investigator designees one of whom is considered to be a specialist with expertise in oncology, a Sponsor representative(s), a pharmacovigilance representative, and a statistician. Additional members may be added to the CRC as appropriate. The CRC is responsible for reviewing and evaluating safety data after each cohort has completed 28 days of treatment (Cycle 1) and subsequently at regularly scheduled meetings as outlined in the cohort review meeting guidelines. The CRC 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 CRC will also be responsible for the initiation of enrollment to the next dose level and confirmation of escalation to the next approved dose level. The CRC will recommend, and the Sponsor’s CMO will approve, the doses of ARV-471 to be used in combination with palbociclib in the expanded portion of the Phase 1b. Patient safety will be monitored by the SRC established in Part B.

1.2 Overall Study Schema

Figure 4 Overall Study Schema



Abbreviations: AE=adverse event; CRC=Cohort Review Committee; D/C=discontinuation; QD=once daily.

1.3 Schedule of Activities

Table 1 Schedule of Activities for Part A – Phase 1 Dose Escalation

Note: As of implementation of Protocol Amendment 6, patients enrolled in Part A who have been on treatment longer than 6 months (met study primary completion date) will switch to the new Schedule of Activities in [Table 8](#) for reduced assessments.

Part A – Phase 1 Dose Escalation											
Procedures	Screening (≤28 days prior C1D1) ¹	Study Treatment Period 1 Cycle (C) = 28 days Starting Dose = 30 mg PO QD							CT/MRI	End of Treatment/ Withdrawal ²	Follow-Up (28 to 35 days) ³
		Cycle 1					Cycles 2 and beyond		Cycle 1 and beyond		
Treatment Day (Visit Window)		Day 1	Day 2	Day 8 (±2)	Day 15 (±2)	Day 21/ Day 28 (±2)	Day 15 (±2) ²⁷	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Informed consent ⁴	X										
Medical/oncologic history ⁵	X										
PE ⁶	X									X	
Abbreviated PE ⁶		X		X		X	X	X			X
Height	X										
Weight	X	X						X		X	
Vital signs ⁷	X	X	X	X	X	X	X	X		X	
ECOG status ⁸	X	X						X		X	X
Hematology ⁹	X	X		X	X	X	X	X		X	

Part A – Phase 1 Dose Escalation											
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days Starting Dose = 30 mg PO QD							CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1					Cycles 2 and beyond		Cycle 1 and beyond		
		Day 1	Day 2	Day 8 (±2)	Day 15 (±2)	Day 21/ Day 28 (±2)	Day 15 (±2)²⁷	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Blood chemistry ¹⁰	X	X		X	X	X	X	X		X	
Coagulation ¹¹	X	X				X*		X		X	
Thyroid function ¹²	X										
Urinalysis ¹³	X	X								X	
Viral disease screening ¹⁴	X										
Pregnancy test and contraceptive check ¹⁵	X	X				X*		X		X	X
Enrollment ¹⁶		X									
ARV-471 ¹⁷		X	X	X	X	X	X	X			
Compliance/ patient diary ¹⁸		X	X	X	X	X	X	X		X	
CT/MRI scans ¹⁹	X								X	X	
Bone scan ²⁰	X										

Part A – Phase 1 Dose Escalation											
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days Starting Dose = 30 mg PO QD							CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1					Cycles 2 and beyond		Cycle 1 and beyond		
		Day 1	Day 2	Day 8 (±2)	Day 15 (±2)	Day 21/ Day 28 (±2)	Day 15 (±2)²⁷	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Tumor markers (CA 15-3, CA 27.29, CEA) and ESR1 mutational status ²¹	X								X ²¹		
ctDNA ²²	X	X				X*		X		X	
Tumor biopsy ²³	X					X*					
AE/SAE monitoring ²⁴	X	X	X	X	X	X	X	X		X	X
Concomitant treatment(s) ²⁵	X	X	X	X	X	X	X	X		X	X
Collection of survival status ²⁶										X	
PK, ECG and ECHO	X	See Pharmacokinetic, ECG and Echocardiogram Sampling Schedule in Table 5 .									

Abbreviations: AE=adverse event; C=Cycle; CA=cancer antigen; CEA=carcinoembryonic antigen; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=Day, ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOT=End of Treatment; ER=estrogen receptor; ESR1=estrogen receptor 1; mBC=metastatic breast cancer; MRI=magnetic resonance imaging;

PE=physical examination; PK=pharmacokinetics; PO=per oral; QD=once daily; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; SAE=serious adverse event

Note: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their dose, which will be administered by study staff onsite. Acceptable time windows for performing each assessment are described in the column headers. One (1) cycle consists of 28 days. Day 28 assessments = Day 1 assessments for the next patient cycle.

Assessments with an asterisk () on Day 21/Day 28 do not have to be performed on Day 21, only on Day 28. The study treatment period is ongoing as long as the patient is receiving ARV-471.

1. Screening is to be obtained within 28 days prior to C1D1 (standard of care activities may be utilized prior to consent).
2. End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
3. Follow-up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, patients will return to undergo review of concomitant medications, ECOG performance status, abbreviated PE, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
4. Informed consent must be obtained prior to undergoing any study-specific procedures.
5. Medical/oncologic and tumor history includes history of disease process (eg, staging) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
6. Physical examinations may be performed within 48 hours prior to a scheduled visit. A full PE is required at Screening and End of Treatment visits. An abbreviated PE should be performed at other visits as indicated. There is no need to repeat PE if baseline assessment is within 96 hours of C1D1. An abbreviated PE will be symptom directed.
7. Vital Signs includes temperature, blood pressure, respiratory rate and pulse rate. Blood pressure and pulse rate should be recorded in the sitting or semi-recumbent position after 5 minutes of rest (recommended same position should be used throughout the study). On in-clinic dosing days, vital signs should be measured prior to dosing (pre-dose). Blood pressure and pulse rate will be repeated 1 hour (± 5 minutes) after dosing during Cycle 1.
8. Patients must have an ECOG performance status of 0 or 1 to be eligible. See [Appendix 7](#) for more information.
9. Hematology: There is no need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. Assessments performed at each subsequent visit should be performed within 48 hours prior to dosing. See [Appendix 3](#) for more information.
10. Blood chemistry: There is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to that date. See [Appendix 3](#) for more information.
11. Coagulation: There is no need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. Day 21/Day 28 does not have to be performed on Day 21, only on Day 28. See [Appendix 3](#) for details.
12. Laboratory assessment for thyroid function (ie, thyroid-stimulating hormone).
13. Urine dipstick testing is acceptable at Screening and End of Treatment visit. There is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to that date. See [Appendix 3](#) for more information.
14. Viral disease screening: Hepatitis B virus surface antigen, hepatitis B core antibody, hepatitis B surface antibody, hepatitis C virus antibodies, and human immunodeficiency virus testing to be conducted by local laboratory when required by local regulations or if warranted by patient history.

15. A serum pregnancy test will be conducted on all women of childbearing potential at Screening. Urine pregnancy tests will be done on study. Contraceptive check: The Investigator or qualified designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or qualified designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected of the patient or the patient's partner. Male patients who are able to father children will need to affirm that they meet the criteria for the correct use of 2 of the selected methods of contraception ([Table 26](#)).
16. Enrollment: Dose level allocation assigned by the Sponsor (or designee) may occur up to 3 days prior to patients Day 1 visit to allow for drug preparation.
17. Study drug treatment: ARV-471 will be administered orally once or twice daily with food during each 28-day cycle. On days of scheduled clinic visits, study drug treatment should be undertaken in the clinic (ie, not at home). Time of dose should be recorded in the source documents and eCRF. On Day 1 and Day 15 patients will be provided a light meal prior to their ARV-471 dose given in the clinic. On additional clinic visit days patients may also be provided a light meal prior to their ARV-471 dose given in the clinic. Patients will self-dose as described above, except for doses that will be administered at study site.
18. Compliance/patient diary: Patients will be required to return all bottles and remaining tablets of ARV-471, as well as the completed patient diary for drug accountability and documentation of food consumption. Patients are to complete patient diary daily during study participation. Patients exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen. Noncompliance is defined as taking less than 80% or more than 120% of assigned study drug during any evaluation period (visit to visit).
19. Tumor assessments (CT/MRI): will be performed within 28 days prior to the first dose of study drug and will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans (same modality should be used throughout the study). If MRI is performed for the abdomen and pelvis examinations at baseline, then at least a non-contrast CT of the chest must be performed as well. CT or MRI scans to be done every 8 weeks (± 5 days) from the date of first dose (Cycle 1 Day 1), for the first 24 weeks of study treatment, then every 12 weeks (± 5 days) thereafter. Scans should be performed independent of dose delays. Tumor assessments will continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST 1.1, study drug discontinuation (for patients who discontinued treatment for reasons other than RECIST-defined disease progression), initiation of new anti-cancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Given the exploratory nature of the study, confirmation of response (CR or PR) is preferred (see [Appendix 8](#)). Tumor assessments should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation.
20. Bone scans must be performed in all patients at baseline within 28 days prior to Cycle 1 Day 1. Bone scans performed >28 to 45 days prior to enrollment as part of clinical care unrelated to this study may be acceptable pending discussion with the Medical Monitor. For patients with bone lesions identified only by bone scan at baseline, additional studies (eg, X-ray, CT scan with bone windows or MRI) must be performed of these lesions at baseline and for follow-up assessments.
21. Tumor markers (CA 15-3, CA 27.29, CEA): will be assessed at baseline. Only elevated markers will be followed on study and timing should coincide with radiographic assessments. Historical ESR1 mutational status performed locally will be collected at Screening when available.
22. ctDNA will be isolated from plasma and analyzed centrally to determine ESR1 mutational status. The Day 21/Day 28 assessment does not have to be performed on Day 21, only on Day 28.
23. Tumor biopsy: If a patient has a tumor accessible for biopsy at a metastatic site of disease a biopsy must be done at Screening and at end of Cycle 1 but no later than end of Cycle 2 visit. Samples will be analyzed centrally by IHC for ER, progesterone receptor, and Ki-67. ESR1 mutational status will be assessed if sufficient tissue is available. The Day 21/Day 28 assessment does not have to be performed on Day 21, only on Day 28. An EOT biopsy should only be performed if a screening biopsy was performed and an on-treatment biopsy was NOT performed at the end of Cycle 1 or before Cycle 2. This EOT biopsy should be performed while the patient is still on study drug.

24. AEs should be documented and recorded at each visit using the NCI CTCAE version 5.0. The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each patient begins from the time the patient provides informed consent through and including a minimum of 30 calendar days after the last study drug administration. If the patient begins a new anti-cancer therapy, the period for recording non-serious AEs on the eCRF ends at the time the new treatment is started. However, any SAEs related to study treatment occurring during the active collection period must still be reported to the Sponsor or designee and recorded in the eCRF, irrespective of any intervening treatment.
25. Concomitant treatments: All concomitant medications, over-the-counter, and nondrug supportive interventions should be recorded in the eCRF including supportive care drugs; eg, anti-emetic treatment and prophylaxis, palliative radiotherapy on study is permitted (eg, skeletal administration for mBC), drugs used to treat AEs or chronic diseases, and nondrug supportive interventions (eg, infusions).
26. Survival visits will occur every 3 months from EOT/Follow-up visit (whichever occurred later) until death, lost to follow-up, or withdrawal of consent. This visit may be performed by phone contact or office visit.
27. The Day 15 (± 2) visit only applies through Cycle 6. From Cycle 7 and beyond, patients will attend follow-up visits once per cycle, on Day 28 (± 2).

Table 2 Schedule of Activities for Part B – Phase 2 Cohort Expansion

No patients remain on study treatment in Part B as of Protocol Amendment 6. Part B patients will switch to the new Schedule of Activities in [Table 9](#) to only be followed for survival as of implementation of Protocol Amendment 6.

Part B – Phase 2 Cohort Expansion									
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C)=28 days Cohort B1 starting dose: 200 mg QD Cohort B2 starting dose: 500 mg QD					CT/MRI	End of Treatment/Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1				Cycles 2 and beyond	Cycle 1 and beyond		
		Day 1	Day 2	Day 15 (±2)	Day 28 (±2)	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Informed consent ⁴	X								
Medical/oncologic history ⁵	X								
PE ₆	X							X	
Abbreviated PE ⁶		X	X	X	X	X			X
Height	X								
Weight	X	X				X		X	
Vital signs ⁷	X	X	X	X	X	X		X	
ECOG status ⁸	X	X				X		X	X
Hematology ⁹	X	X			X	X		X	

Part B – Phase 2 Cohort Expansion									
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C)=28 days Cohort B1 starting dose: 200 mg QD Cohort B2 starting dose: 500 mg QD					CT/MRI	End of Treatment/Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1				Cycles 2 and beyond	Cycle 1 and beyond		
Treatment Day (Visit Window)		Day 1	Day 2	Day 15 (±2)	Day 28 (±2)	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Blood chemistry ¹⁰	X	X			X	X		X	
Coagulation ¹¹	X	X			X	X		X	
Urinalysis ¹²	X	X						X	
Viral disease screening ¹³	X								
Pregnancy test and contraceptive check ¹⁴	X	X			X	X		X	X
Enrollment ¹⁵		X							
ARV-471 ¹⁶		X	X	X	X	X			
Compliance/ patient diary ¹⁷		X	X	X	X	X		X	
CT/MRI scans ¹⁸	X						X	X	
Bone scan ¹⁹	X								

Part B – Phase 2 Cohort Expansion									
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C)=28 days Cohort B1 starting dose: 200 mg QD Cohort B2 starting dose: 500 mg QD				CT/MRI	End of Treatment/Withdrawal²	Follow-Up (28 to 35 days)³	
		Cycle 1				Cycles 2 and beyond	Cycle 1 and beyond		
		Day 1	Day 2	Day 15 (±2)	Day 28 (±2)	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Tumor markers (CA 15-3, CA 27.29, CEA) and ESR1 mutational status ²⁰	X						X ²⁰		
ctDNA ²¹	X	X			X	X		X	
Tumor biopsy ²²	X				X				
AE/SAE monitoring ²³	X	X	X	X	X	X		X	X
Concomitant treatment(s) ²⁴	X	X	X	X	X	X		X	X
Collection of survival status ²⁵								X	
PK, ECG and ECHO	X	See Pharmacokinetic, ECG and Echocardiogram Sampling Schedule in Table 7 .							

Abbreviations: AE=adverse event; C=Cycle; CA=cancer antigen; CEA=carcinoembryonic antigen; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=Day, ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOT=End of Treatment; ER=estrogen receptor; ESR1=estrogen receptor 1; mBC=metastatic breast cancer; MRI=magnetic resonance imaging;

PE=physical examination; PK=pharmacokinetics; PO=per oral; QD=once daily; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; SAE=serious adverse event.

***Note:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their dose, which will be administered by study staff onsite. Acceptable time windows for performing each assessment are described in the column headers. One (1) cycle consists of 28 days. Day 28 assessments=Day 1 assessments for the next patient cycle. The study treatment period is ongoing as long as the patient is receiving ARV-471.

1. Screening is to be obtained within 28 days prior to C1D1 (standard of care activities may be utilized prior to consent).
2. End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments). Imaging should be repeated at EOT for any patients who would have been due for the week 24 imaging at the time of EOT, and where radiographic progression has not yet been documented.
3. Follow-up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, patients will return to undergo review of concomitant medications, ECOG performance status, abbreviated PE, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
4. Informed consent must be obtained prior to undergoing any study specific procedures.
5. Medical/oncologic and tumor history includes history of disease process (eg, staging) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
6. Physical examinations may be performed within 48 hours prior to a scheduled visit. A full PE is required at Screening and abbreviated PEs should be performed as appropriate at each visit where complete PEs are not required. If the Screening assessment is within 96 hours of C1D1, a PE on C1D1 is not required to be repeated. An abbreviated PE will be symptom directed.
7. Vital signs include temperature, blood pressure, respiratory rate and pulse rate. Blood pressure and pulse rate should be recorded in the sitting or semi-recumbent position after 5 minutes of rest (recommended same position should be used throughout the study). On in-clinic dosing days, vital signs should be measured prior to dosing (pre-dose). Blood pressure and pulse rate will be repeated 1 hour (± 5 minutes) after dosing during Cycle 1.
8. Patients must have an ECOG performance status of 0 or 1 to be eligible. See [Appendix 7](#) for more information.
9. Hematology: There is no need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. Assessments performed at each subsequent visit should be performed within 48 hours prior to dosing. See [Appendix 3](#) for more information.
10. Blood chemistry: There is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to that date. See [Appendix 3](#) for more information.
11. Coagulation: There is no need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. See [Appendix 3](#) for details.
12. Urine dipstick testing is acceptable at Screening and End-of-Treatment visit. There is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to that date. See [Appendix 3](#) for more information.
13. Viral disease screening: Hepatitis B virus surface antigen, hepatitis B core antibody, hepatitis B surface antibody, hepatitis C virus antibodies, and human immunodeficiency virus testing to be conducted by local laboratory when required by local regulations or if warranted by patient history.

14. A serum pregnancy test will be conducted on all women of childbearing potential at Screening. Urine pregnancy tests will be done on study. Contraceptive check: The Investigator or qualified designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or qualified designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected of the patient or the patient's partner. Male patients who are able to father children will need to affirm that they meet the criteria for the correct use of 2 of the selected methods of contraception (Table 26).
15. Enrollment: Dose level assigned by the Sponsor (or designee) may occur up to 3 days prior to patients Day 1 visit to allow for drug preparation.
16. Study drug treatment: ARV-471 will be administered orally once or twice daily with food during each 28-day cycle. On days of scheduled clinic visits, study drug treatment should be undertaken in the clinic (ie, not at home). Time of dose should be recorded in the source documents and eCRF. Patients will self-dose as described above, except for doses that will be administered at study site.
17. Compliance/patient diary: Patients will be required to return all bottles and remaining tablets of ARV-471, as well as the completed patient diary for drug accountability and documentation of food consumption. Patients are to complete patient diary daily during study participation. Patients exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen. Noncompliance is defined as taking less than 80% or more than 120% of assigned study drug during any evaluation period (visit to visit).
18. Tumor assessments (CT/MRI) will be performed within 28 days prior to the first dose of study drug and will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans (same modality should be used throughout the study). If MRI is performed for the abdomen and pelvis examinations at baseline, then at least a non-contrast CT of the chest must be performed as well. CT or MRI scans to be done every 8 weeks (± 5 days) from the date of first dose (Cycle 1 Day 1), for the first 24 weeks of study treatment, then every 12 weeks (± 5 days) thereafter. Scans should be performed independent of dose delays. Week 24 scan should be performed on time (± 5 days) from the date of first dose as it supports the primary end point (Clinical Benefit Rate) of Part B. Tumor assessments will continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST 1.1, study drug discontinuation (for patients who discontinued treatment for reasons other than RECIST defined disease progression), initiation of new anti-cancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Given the exploratory nature of the study, confirmation of response (complete response or partial response) is preferred. Tumor assessments should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation.
19. Bone scans must be performed in all patients at baseline within 28 days prior to Cycle 1 Day 1. If bone scans are not available or cannot be scheduled readily, CT/MRI scan with bone windows can be sufficient. Bone scans performed >28 to 45 days prior to enrollment as part of clinical care unrelated to this study may be acceptable pending discussion with the Medical Monitor. For patients with bone lesions identified only by bone scan at baseline, additional studies (eg, X-ray, CT scan with bone windows or MRI) must be performed of these lesions at baseline and for all follow-up assessments.
20. Tumor markers (CA 15-3, CA 27.29, CEA) will be assessed at baseline. Only elevated markers will be followed on study and timing should coincide with radiographic assessments. Historical ESR1 mutational status performed locally will be collected at Screening when available.
21. ctDNA will be isolated from plasma and analyzed centrally and used to determine ESR1 mutational status.
22. Tumor biopsy: If a patient has a tumor accessible for biopsy at a metastatic site of disease a biopsy must be done at Screening and at end of Cycle 1 but no later than end of Cycle 2 visit. Samples will be analyzed centrally by immunohistochemistry for ER, progesterone receptor, and Ki-67. ESR1 mutational status will be assessed if sufficient tissue is available. Biopsy sites that are soft tissue tumor lesions or accessible visceral disease that can be biopsied with acceptable clinical risk (as judged by the Investigator) are preferred. Biopsy of bone lesions should be discussed with the Medical Monitor. Biopsy sites should be distinct from RECIST 1.1 target lesions. Two to four core needle biopsies should be obtained at each time point per institutional procedure using an 18-gauge or larger core needle. Additional details on biopsy collection and processing will be provided in the laboratory manual.

23. Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each patient begins from the time the patient provides informed consent through and including a minimum of 30 calendar days after the last study drug administration. If the patient begins a new anti-cancer therapy, the period for recording non-serious AEs on the eCRF ends at the time the new treatment is started. However, any SAEs related to study treatment occurring during the active collection period must still be reported to the Sponsor or designee and recorded in the eCRF, irrespective of any intervening treatment.
24. Concomitant treatments: All concomitant medications, over the counter, and nondrug supportive interventions should be recorded in the eCRF including supportive care drugs; eg, antiemetic treatment and prophylaxis, palliative radiotherapy on study is permitted (eg, skeletal administration for mBC), drugs used to treat AEs or chronic diseases, and nondrug supportive interventions (eg, infusions).
25. Survival visits will occur every 3 months from EOT/Follow-up visit (whichever occurred later) until death, lost to follow-up, or withdrawal of consent. This visit may be performed by phone contact or office visit.

Table 3 Schedule of Activities for Part C Cohorts C1-C4 – Combination ARV-471 + Palbociclib

Note: As of implementation of Protocol Amendment 6, patients enrolled in Part C Cohorts C1-C4 who have been on treatment longer than 6 months (met study primary completion date) will switch to the new Schedule of Activities [Table 10](#) for reduced assessments.

Part C Cohorts C1-C4 – Phase 1b Combination ARV-471 + Palbociclib											
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days ARV-471 Starting Dose = 200 mg PO QD Palbociclib Starting Dose = 125 mg PO QD for 21D, 7D off							CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1					Cycles 2 and beyond		Cycle 1 and beyond		
Treatment Day (Visit Window)		Day 1	Day 2	Day 8 (±2)	Day 15 (±2)	Day 21/ Day 28 (±2)	Day 15 (±2)²⁷	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Informed consent ⁴	X										
Medical/oncologic history ⁵	X										
PE ⁶	X									X	
Abbreviated PE ⁶		X		X		X	X	X			X
Height	X										
Weight	X	X						X		X	
Vital signs ⁷	X	X	X	X	X	X	X	X		X	
ECOG status ⁸	X	X						X		X	X
Hematology ⁹	X	X			X	X (D28 only)	X	X		X	

Part C Cohorts C1-C4 – Phase 1b Combination ARV-471 + Palbociclib											
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days ARV-471 Starting Dose = 200 mg PO QD Palbociclib Starting Dose = 125 mg PO QD for 21D, 7D off							CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1					Cycles 2 and beyond		Cycle 1 and beyond		
		Day 1	Day 2	Day 8 (±2)	Day 15 (±2)	Day 21/ Day 28 (±2)	Day 15 (±2)²⁷	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Blood chemistry ¹⁰	X	X		X	X	X	X	X		X	
Coagulation ¹¹	X	X				X*		X		X	
Thyroid function ¹²	X										
Urinalysis ¹³	X	X								X	
Viral disease screening ¹⁴	X										
Pregnancy test and contraceptive check ¹⁵	X	X				X*		X		X	X
Enrollment ¹⁶		X									

Part C Cohorts C1-C4 – Phase 1b Combination ARV-471 + Palbociclib											
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days ARV-471 Starting Dose = 200 mg PO QD Palbociclib Starting Dose = 125 mg PO QD for 21D, 7D off							CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1					Cycles 2 and beyond		Cycle 1 and beyond		
		Day 1	Day 2	Day 8 (±2)	Day 15 (±2)	Day 21/ Day 28 (±2)	Day 15 (±2)²⁷	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
ARV-471 ¹⁷ administration		X (once or twice daily)									
Palbociclib ¹⁷ administration		X (once daily)				X (Day 21 only, followed by 7 days off)	X (once daily for 21 days, followed by 7 days off)				
Compliance/ patient diary ¹⁸		X	X	X	X	X	X	X		X	
CT/MRI scans ¹⁹	X								X	X	
Bone scan ²⁰	X										
Tumor markers (CA 15-3, CA 27.29, CEA) and ESR1 mutational status ²¹	X								X ²¹		

Part C Cohorts C1-C4 – Phase 1b Combination ARV-471 + Palbociclib											
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days ARV-471 Starting Dose = 200 mg PO QD Palbociclib Starting Dose = 125 mg PO QD for 21D, 7D off							CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1					Cycles 2 and beyond		Cycle 1 and beyond		
		Day 1	Day 2	Day 8 (±2)	Day 15 (±2)	Day 21/ Day 28 (±2)	Day 15 (±2)²⁷	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
ctDNA ²²	X	X				X*		X		X	
Tumor biopsy ²³	X					X*					
AE/SAE monitoring ²⁴	X	X	X	X	X	X	X	X		X	X
Concomitant treatment(s) ²⁵	X	X	X	X	X	X	X	X		X	X
Collection of survival status ²⁶										X	
PK, ECG and ECHO	X	See Pharmacokinetic, ECG and Echocardiogram Sampling Schedule in Table 5 .									

Abbreviations: AE=adverse event; C=Cycle; CA=cancer antigen; CEA =carcinoembryonic antigen; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=Day, ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOT=End of Treatment; ER=estrogen receptor; ESR1=estrogen receptor 1; mBC=metastatic breast cancer; MRI=magnetic resonance imaging; PE=physical examination; PK=pharmacokinetics; PO=per oral; QD=once daily; RECIST 1.1= Response Evaluation Criteria In Solid Tumors version 1.1; SAE=serious adverse event.

Note: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their dose, which will be administered by study staff onsite. Acceptable time windows for performing each assessment are described in the column headers. One (1) cycle consists of 28 days. Day 28 assessments = Day 1 assessments for the next patient cycle.

Assessments with an asterisk () on Day 21/Day 28 do not have to be performed on Day 21, only on Day 28. The study treatment period is ongoing as long as the patient is receiving ARV-471.

1. Screening is to be obtained within 28 days prior to C1D1 (standard of care activities may be utilized prior to consent).
2. End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments). Imaging should be repeated at EOT for any patients who would have been due for the week 24 imaging at the time of EOT, and where radiographic progression has not yet been documented.
3. Follow-up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, patients will return to undergo review of concomitant medications, ECOG performance status, abbreviated PE, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
4. Informed consent must be obtained prior to undergoing any study specific procedures.
5. Medical/oncologic and tumor history includes history of disease process (eg, staging) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
6. Physical examinations may be performed within 48 hours prior to a scheduled visit. A full PE is required at Screening and abbreviated PEs should be performed as appropriate at each visit where complete PEs are not required. There is no need to repeat PE if baseline assessment is within 96 hours on C1D1. An abbreviated PE will be symptom directed.
7. Vital Signs includes temperature, blood pressure, respiratory rate and pulse rate. Blood pressure and pulse rate should be recorded in the sitting or semi-recumbent position after 5 minutes of rest (recommended same position should be used throughout the study). On in-clinic dosing days, vital signs should be measured prior to dosing (pre-dose). Blood pressure and pulse rate will be repeated 1 hour (± 5 minutes) after dosing during Cycle 1.
8. Patients must have an ECOG performance status of 0 or 1 to be eligible. See [Appendix 7](#) for more information.
9. Hematology: There is no need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. Assessments performed at each subsequent visit should be performed within 48 hours prior to dosing. For palbociclib, CBC should be performed at the beginning of each cycle (screening labs can count if performed within 72 hours prior to C1D1) and on Day 15 of the first 2 cycles, and as clinically indicated. See [Appendix 3](#) for more information.
10. Blood chemistry: There is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to that date. See [Appendix 3](#) for more information.
11. Coagulation: there is no need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. Day 21/Day 28 does not have to be performed on Day 21, only on Day 28. See [Appendix 3](#) for details.
12. Laboratory assessment for thyroid function (ie, thyroid-stimulating hormone) should be performed at Screening.
13. Urine dipstick testing is acceptable at Screening and End of Treatment visit. There is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to that date. See [Appendix 3](#) for more information.
14. Viral disease screening: Hepatitis B virus surface antigen, hepatitis B core antibody, hepatitis B surface antibody, hepatitis C virus antibodies, and human immunodeficiency virus testing to be conducted by local laboratory when required by local regulations or if warranted by patient history.

15. A serum pregnancy test will be conducted on all women of childbearing potential at Screening. Urine pregnancy tests will be done on study. Contraceptive check: The Investigator or qualified designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or qualified designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected of the patient or the patient's partner. Male patients who are able to father children will need to affirm that they meet the criteria for the correct use of 2 of the selected methods of contraception ([Table 26](#)).
16. Enrollment: Dose level allocation assigned by the Sponsor (or designee) may occur up to 3 days prior to patients Day 1 visit to allow for drug preparation.
17. Study drug treatment: ARV-471 and palbociclib will be administered together orally daily with food at approximately the same time each day during each 28-day cycle. Palbociclib (125 mg) is dosed once daily for 21 days, followed by 7 days off. On days of scheduled clinic visits, study drug treatments should be undertaken in the clinic (ie, not at home). Time of dose should be recorded in the source documents and eCRF. On Day 1 and Day 15, patients will be provided a light meal prior to their ARV-471/palbociclib dose given in the clinic. On additional clinic visit days patients may also be provided a light meal prior to their ARV-471/palbociclib dose given in the clinic. Patients will self-dose as described above, except for doses that will be administered at study site.
18. Compliance/patient diary: patients will be required to return all packaging and remaining tablets of ARV-471 and palbociclib (capsules), as well as the completed patient diary for drug accountability and documentation of food consumption. Patients are to complete patient diary daily during study participation. Patients exhibiting poor adherence as assessed by tablet and/or capsule counts should be counseled on the importance of good compliance to the study dosing regimen. Noncompliance is defined as taking less than 70% or more than 120% of one of the assigned study drugs during any evaluation period (visit to visit).
19. Tumor assessments (CT/MRI): will be performed within 28 days prior to the first dose of study drug and will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans (same modality should be used throughout the study). If MRI is performed for the abdomen and pelvis examinations at baseline, then at least a non-contrast CT of the chest must be performed as well. CT or MRI scans to be done every 8 weeks (± 5 days) from the date of first dose (C1D1), for the first 24 weeks of study treatment, then every 12 weeks (± 5 days) thereafter. Scans should be performed independent of dose delays. Tumor assessments will continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST 1.1, study drug discontinuation (for patients who discontinued treatment for reasons other than RECIST-defined disease progression), initiation of new anti-cancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Given the exploratory nature of the study, confirmation of response (complete response or partial response) is preferred (see [Appendix 8](#)). Tumor assessments should be repeated at the EOT visit if more than 8 weeks have passed since the last evaluation.
20. Bone scans must be performed in all patients at baseline within 28 days prior to C1D1. Bone scans performed >28 to 45 days prior to enrollment as part of clinical care unrelated to this study may be acceptable pending discussion with the Medical Monitor. For patients with bone lesions identified only by bone scan at baseline, additional studies (eg, X-ray, CT scan with bone windows or MRI) must be performed of these lesions for follow-up assessment.
21. Tumor markers (CA 15-3, CA 27.29, CEA): will be assessed at baseline. Only elevated markers will be followed on study and timing should coincide with radiographic assessments. Historical ESR1 mutational status performed locally will be collected at Screening when available.
22. ctDNA will be isolated from plasma and analyzed centrally to determine ESR1 mutational status. The Day 21/Day 28 assessment does not have to be performed on Day 21, only on Day 28.
23. Tumor biopsy: if a patient has a tumor accessible for biopsy at a metastatic site of disease a biopsy must be done at Screening and at end of Cycle 1 but no later than end of Cycle 2 visit. Samples will be analyzed centrally by immunohistochemistry for ER, progesterone receptor, and Ki-67. Mutational status of ESR1 and other genes will be assessed if sufficient tissue is available. The Day 21/Day 28 assessment does not have to be performed on Day 21, only on Day 28. An EOT biopsy should only be performed if a screening biopsy was performed.

24. AEs should be documented and recorded at each visit using the NCI CTCAE version 5.0. The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each patient begins from the time the patient provides informed consent through and including a minimum of 30 calendar days after the last study drug administration. If the patient begins a new anti-cancer therapy, the period for recording non-serious AEs on the eCRF ends at the time the new treatment is started. However, any SAEs related to study treatment occurring during the active collection period must still be reported to the Sponsor or designee and recorded in the eCRF, irrespective of any intervening treatment.
25. Concomitant treatments: all concomitant medications, over-the-counter, and nondrug supportive interventions should be recorded in the eCRF including supportive care drugs; eg, anti-emetic treatment and prophylaxis, palliative radiotherapy on study is permitted (eg, skeletal administration for mBC), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, infusions).
26. Survival visits will occur every 3 months from EOT/Follow-up visit (whichever occurred later) until death, lost to follow-up, or withdrawal of consent. This visit may be performed by phone contact or office visit.
27. The Day 15 (± 2) visit only applies through Cycle 6. From Cycle 7 and beyond, patients will attend follow-up visits once per cycle, on Day 28 (± 2).

Table 4 Schedule of Activities for Part C Cohort C5 ONLY

Note: As of implementation of Protocol Amendment 6, patients enrolled in Part C Cohort C5 who have been on treatment longer than 6 months (met study primary completion date) will switch to the new Schedule of Activities in [Table 10](#) for reduced assessments.

Part C Cohort C5 ONLY – Phase 1b Combination ARV-471 + Palbociclib										
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days ARV-471 Starting Dose = 200 mg PO QD, starting C1D9 Palbociclib Starting Dose = 100 mg PO QD starting C1D1 for 21D, 7D off						CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1				Cycles 2 and beyond		Cycle 1 and beyond		
Treatment Day (Visit Window)		Day 1	Day 8 (-1)	Day 15 (±2)	Day 21 (-1)/ Day 28 (±2)	Day 15 (±2)⁴	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Informed consent ⁵	X									
Medical/oncologic history ⁶	X									
PE ⁷	X								X	
Abbreviated PE ⁷		X	X		X	X	X			X
Height	X									
Weight	X	X					X		X	
Vital signs ⁸	X	X	X	X	X	X	X		X	
ECOG status ⁹	X	X					X		X	X
Hematology ¹⁰	X	X	X	X	X	X	X		X	

Part C Cohort C5 ONLY – Phase 1b Combination ARV-471 + Palbociclib										
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days ARV-471 Starting Dose = 200 mg PO QD, starting C1D9 Palbociclib Starting Dose = 100 mg PO QD starting C1D1 for 21D, 7D off						CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1				Cycles 2 and beyond		Cycle 1 and beyond		
Treatment Day (Visit Window)		Day 1	Day 8 (-1)	Day 15 (±2)	Day 21 (-1)/ Day 28 (±2)	Day 15 (±2)⁴	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Blood chemistry ¹¹	X	X	X	X	X	X	X		X	
Coagulation ¹²	X	X			X*		X		X	
Thyroid function ¹³	X									
Urinalysis ¹⁴	X	X							X	
Viral disease screening ¹⁵	X									
Pregnancy test and contraceptive check ¹⁶	X	X			X*		X		X	X
Enrollment ¹⁷		X								
ARV-471 ¹⁸ administration				←←←←←←←←←← X →→→→→→→→→→ (once daily starting C1D9)						

Part C Cohort C5 ONLY – Phase 1b Combination ARV-471 + Palbociclib										
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days ARV-471 Starting Dose = 200 mg PO QD, starting C1D9 Palbociclib Starting Dose = 100 mg PO QD starting C1D1 for 21D, 7D off						CT/MRI	End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³
		Cycle 1				Cycles 2 and beyond		Cycle 1 and beyond		
Treatment Day (Visit Window)		Day 1	Day 8 (-1)	Day 15 (±2)	Day 21 (-1)/ Day 28 (±2)	Day 15 (±2)⁴	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Palbociclib ¹⁸ administration		←←←←← X →→→→→ (once daily)				X (Day 21 only, followed by 7 days off)	X (once daily for 21 days, followed by 7 days off)			
Compliance/ patient diary ¹⁹		X	X	X	X	X	X		X	
CT/MRI scans ²⁰	X							X	X	
Bone scan ²¹	X									
Tumor markers (CA 15-3, CA 27.29, CEA) and ESR1 mutational status ²²	X							X ²²		
ctDNA ²³	X	X			X*		X		X	
AE/SAE monitoring ²⁴	X	X	X	X	X	X	X		X	X

Part C Cohort C5 ONLY – Phase 1b Combination ARV-471 + Palbociclib										
Procedures	Screening (≤28 days prior C1D1)¹	Study Treatment Period 1 Cycle (C) = 28 days ARV-471 Starting Dose = 200 mg PO QD, starting C1D9 Palbociclib Starting Dose = 100 mg PO QD starting C1D1 for 21D, 7D off				CT/MRI		End of Treatment/ Withdrawal²	Follow-Up (28 to 35 days)³	
		Cycle 1				Cycles 2 and beyond		Cycle 1 and beyond		
Treatment Day (Visit Window)		Day 1	Day 8 (-1)	Day 15 (±2)	Day 21 (-1)/ Day 28 (±2)	Day 15 (±2)⁴	Day 28 (±2)	Every 8 weeks from C1D1 (±5 days)		
Concomitant treatment(s) ²⁵	X	X	X	X	X	X	X		X	X
PK, ECG and ECHO	X	See Pharmacokinetic, ECG and Echocardiogram Sampling Schedule in Table 6 .								

Abbreviations: AE=adverse event; C=Cycle; CA=cancer antigen; CBC = complete blood count; CEA =carcinoembryonic antigen; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=Day, ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOT=End of Treatment; ER=estrogen receptor; ESR1=estrogen receptor 1; mBC=metastatic breast cancer; MRI=magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PE=physical examination; PK=pharmacokinetics; PO=per oral; QD=once daily; RECIST 1.1= Response Evaluation Criteria In Solid Tumors version 1.1; SAE=serious adverse event.

Note: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. On mornings where patients are in the clinic, they will be instructed to hold their dose, which will be administered by study staff onsite. Acceptable time windows for performing each assessment are described in the column headers. One (1) cycle consists of 28 days. Day 28 assessments = Day 1 assessments for the next patient cycle.

Assessments with an asterisk () on Day 21/Day 28 do not have to be performed on Day 21, only on Day 28. The study treatment period is ongoing as long as the patient is receiving ARV-471.

1. Screening is to be obtained within 28 days prior to C1D1 (standard of care activities may be utilized prior to consent).
2. End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments). Imaging should be repeated at EOT for any patients who would have been due for the week 24 imaging at the time of EOT, and where radiographic progression has not yet been documented.

3. Follow-up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, patients will return to undergo review of concomitant medications, ECOG performance status, abbreviated PE, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
4. The Day 15 (± 2) visit only applies through Cycle 6. From Cycle 7 and beyond, patients will attend follow-up visits once per cycle, on Day 28 (± 2).
5. Informed consent must be obtained prior to undergoing any study specific procedures.
6. Medical/oncologic and tumor history includes history of disease process (eg, staging) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
7. Physical examinations may be performed within 48 hours prior to a scheduled visit. A full PE is required at Screening and abbreviated PEs should be performed as appropriate at each visit where complete PEs are not required. There is no need to repeat PE if baseline assessment is within 96 hours on C1D1. An abbreviated PE will be symptom directed.
8. Vital Signs include temperature, blood pressure, respiratory rate, and pulse rate. Blood pressure and pulse rate should be recorded in the sitting or semi-recumbent position after 5 minutes of rest (recommended same position should be used throughout the study). On in-clinic dosing days, vital signs should be measured prior to dosing (pre-dose). Blood pressure and pulse rate will be repeated 1 hour (± 5 minutes) after dosing during Cycle 1.
9. Patients must have an ECOG performance status of 0 or 1 to be eligible. See [Appendix 7](#) for more information.
10. Hematology: There is no need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. Assessments performed at each subsequent visit should be performed within 48 hours prior to dosing. For palbociclib, CBC should be performed at the beginning of each cycle (screening labs can count if performed within 72 hours prior to C1D1) and on Day 15 of the first 2 cycles, and as clinically indicated. See [Appendix 3](#) for more information.
11. Blood chemistry: There is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to that date. See [Appendix 3](#) for more information.
12. Coagulation: there is no need to repeat on C1D1 if baseline assessment is performed within 72 hours prior to that date. Day 21/Day 28 does not have to be performed on Day 21, only on Day 28. See [Appendix 3](#) for details.
13. Laboratory assessment for thyroid function (ie, thyroid-stimulating hormone) should be performed at Screening.
14. Urine dipstick testing is acceptable at Screening and End of Treatment visit. There is no need to repeat on C1D1 if baseline assessment is performed within 7 days prior to that date. See [Appendix 3](#) for more information.
15. Viral disease screening: Hepatitis B virus surface antigen, hepatitis B core antibody, hepatitis B surface antibody, hepatitis C virus antibodies, and human immunodeficiency virus testing to be conducted by local laboratory when required by local regulations or if warranted by patient history.
16. A serum pregnancy test will be conducted on all women of childbearing potential at Screening. Urine pregnancy tests will be done on study. Contraceptive check: The Investigator or qualified designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or qualified designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected of the patient or the patient's partner. Male patients who are able to father children will need to affirm that they meet the criteria for the correct use of 2 of the selected methods of contraception ([Table 26](#)).
17. Enrollment: Dose level allocation assigned by the Sponsor (or designee) may occur up to 3 days prior to patients Day 1 visit to allow for drug preparation.

18. Study drug treatment: Palbociclib (100 mg) is dosed once daily starting on C1D1 for 21 days, followed by 7 days off. Dosing of ARV-471 will begin on Cycle 1 Day 9 and once daily dosing of ARV-471 will continue until the end of study. Palbociclib and/or ARV-471 will be administered with food at approximately the same time each day, in the morning. There is no clinic visit on Day 9, so patients will be sent home with ARV-471 on Day 8 with instructions to begin once daily dosing on Cycle 1 Day 9. On days of scheduled clinic visits, study drug treatments should be undertaken in the clinic (ie, not at home). Time of dose should be recorded in the source documents and eCRF. On Day 8 and Day 21, patients will be provided a light meal prior to their ARV-471/palbociclib dose given in the clinic. On additional clinic visit days patients may also be provided a light meal prior to their ARV-471/palbociclib dose given in the clinic. Patients will self-dose as described above, except for doses that will be administered at study site.
19. Compliance/patient diary: patients will be required to return all packaging and remaining tablets of ARV-471 and palbociclib (capsules), as well as the completed patient diary for drug accountability and documentation of food consumption. Patients are to complete patient diary daily during study participation. Patients exhibiting poor adherence as assessed by tablet and/or capsule counts should be counseled on the importance of good compliance to the study dosing regimen. Noncompliance is defined as taking less than 70% or more than 120% of one of the assigned study drugs during any evaluation period (visit to visit).
20. Tumor assessments (CT/MRI): will be performed within 28 days prior to the first dose of study drug and will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans (same modality should be used throughout the study). If MRI is performed for the abdomen and pelvis examinations at baseline, then at least a non-contrast CT of the chest must be performed as well. CT or MRI scans to be done every 8 weeks (± 5 days) from the date of first dose (C1D1), for the first 24 weeks of study treatment, then every 12 weeks (± 5 days) thereafter. Scans should be performed independent of dose delays. Tumor assessments will continue until radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST 1.1, study drug discontinuation (for patients who discontinued treatment for reasons other than RECIST-defined disease progression), initiation of new anti-cancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Given the exploratory nature of the study, confirmation of response (complete response or partial response) is preferred (see [Appendix 8](#)). Tumor assessments should be repeated at the EOT visit if more than 8 weeks have passed since the last evaluation.
21. Bone scans must be performed in all patients at baseline within 28 days prior to C1D1. Bone scans performed >28 to 45 days prior to enrollment as part of clinical care unrelated to this study may be acceptable pending discussion with the Medical Monitor. For patients with bone lesions identified only by bone scan at baseline, additional studies (eg, X-ray, CT scan with bone windows or MRI) must be performed of these lesions for follow-up assessment.
22. Tumor markers (CA 15-3, CA 27.29, CEA): will be assessed at baseline. Only elevated markers will be followed on study and timing should coincide with radiographic assessments. Historical ESR1 mutational status performed locally will be collected at Screening when available.
23. ctDNA will be isolated from plasma and analyzed centrally to determine ESR1 mutational status. The Day 21/Day 28 assessment does not have to be performed on Day 21, only on Day 28.
24. AEs should be documented and recorded at each visit using the NCI CTCAE version 5.0. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 30 calendar days after the last study drug administration. If the patient begins a new anti-cancer therapy, the period for recording non-serious AEs on the eCRF ends at the time the new treatment is started. However, any SAEs related to study treatment occurring during the active collection period must still be reported to the Sponsor or designee and recorded in the eCRF, irrespective of any intervening treatment.
25. Concomitant treatments: all concomitant medications, over-the-counter, and nondrug supportive interventions should be recorded in the eCRF including supportive care drugs; eg, anti-emetic treatment and prophylaxis, palliative radiotherapy on study is permitted (eg, skeletal administration for mBC), drugs used to treat AEs or chronic diseases, and non-drug supportive interventions (eg, infusions).

Table 5 Schedule for PK and ECG Assessments for Part A and Part C (Cohorts C1-C4)

Note: As of Administrative Letter 5, PK sample collection is no longer required for active patients on Part A or Part C Cohorts C1-C4 who have received treatment beyond Cycle 6. Please refer to [Table 8](#) and [Table 10](#) for reduced ECG assessment guidance.

Procedures	Screening (≤28 days prior to C1D1)	Study Treatment Period 1 Cycle = 28 days							End of Treatment/ Withdrawal ¹
		Cycle 1					Cycle 2 and beyond		
Visit Identifier (Visit Window)		Day 1	Day 2	Day 8 (±2)	Day 15 (±2)	Day 21(±2)/ Day 28 (±2)	Day 15 (±2) ⁷	Day 28 (±2)	
ARV-471/Palbociclib		X	X	X	X	X	X	X	
Pharmacokinetics ²									
Pre-dose (if dosing day)		X	X	X	X	X	X	X	X ⁶
1 hour (± 6 min)		X			X				
2 hours (± 15 min)		X			X				
4 hours (± 15 min)		X			X				
6 hours (± 15 min)		X			X				
8 hours (± 15 min)		X			X				
12 hours (± 15 min) optional ³		X			X				
Electrocardiogram ⁴									
Pre-dose	X	X	X	X	X	X	X	X	X ⁶
2 hours (±15 min)		X			X				
4 hours (±25 min)		X			X				
Echocardiogram ⁵									
Pre-dose	X								

Abbreviations: C=Cycle; D=Day; ECG=electrocardiogram; QD=once daily; QTcF=corrected QT interval by Fridericia's method; PK=pharmacokinetics.

Note: On days of scheduled clinic visits, study drug treatment should be undertaken in the clinic (ie, not at home).

1. End of Treatment/Withdrawal: visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
2. On Days 1 and 15, the patient will be provided a light meal after the pre-dose sample prior to their ARV-471 dose in the clinic.
3. Collection of PK sample at 12 hours (± 15 min) is optional. Samples are to be collected from patients who remain at the clinic during this time.
4. The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) should be obtained as closely as possible in succession, but no more than 2 minutes apart. All 12-lead ECGs should be confirmed by a qualified person at the institution and may be reviewed by a central laboratory. When coinciding with blood sample draws for PK, ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>60 msec increase from baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
5. Repeat as clinically indicated.
6. A single timepoint assessment can be collected if the patient does not receive study treatment on this visit.
7. The Day 15 (± 2) PK and ECG collection only applies through Cycle 6. From Cycle 7 and beyond, patients will have PK samples collected once per cycle, on Day 28 (± 2).

Table 6 Schedule for PK and ECG Assessments for Part C Cohort C5 ONLY

Note: As of Administrative Letter 5, PK sample collection is no longer required for active patients on Part C Cohort C5 who have received treatment beyond Cycle 6. Please refer to [Table 10](#) for reduced ECG assessment guidance.

Procedures	Screening (≤28 days prior to C1D1)	Study Treatment Period 1 Cycle = 28 days ARV-471 Starting Dose = 200 mg PO QD, starting C1D9 Palbociclib Starting Dose = 100 mg PO QD starting C1D1 for 21D, 7D off							End of Treatment/ Withdrawal ¹
		Cycle 1					Cycle 2 and beyond		
		Visit Identifier (Visit Window)	Day 1	Day 8 (-1)	Day 15 (±2)	Day 21 (-1)	Day 28 (±2)	Day 15 (±2)	Day 28 (±2)
Palbociclib ²		←←←←←←←←← X →→→→→→→→→→ (once daily starting C1D1, for 21 days followed by 7 days off)					X		
ARV-471 ³				←←←←←←←←← X →→→→→→→→→→ (once daily starting C1D9)			X	X	
Pharmacokinetics ⁴									
Pre-dose (if dosing day)			X ⁷	X ⁸	X ⁸	X ⁸	X ^{8, 9}	X ^{8, 9}	
1 hour (± 6 min)			X ⁷		X ⁸				
2 hours (± 15 min)			X ⁷		X ⁸				
4 hours (± 15 min)			X ⁷		X ⁸				
6 hours (± 15 min)			X ⁷		X ⁸				
8 hours (± 15 min)			X ⁷		X ⁸				
Electrocardiogram ⁵									
Pre-dose	X	X	X	X	X	X	X ¹⁰	X	X ¹¹
Echocardiogram ⁶									
Pre-dose	X								

Abbreviations: C=Cycle; D=Day; ECG=electrocardiogram; QD=once daily; QTcF=corrected QT interval by Fridericia's method; PK=pharmacokinetics; PO = oral.

Note: On days of scheduled clinic visits, study drug treatment should be undertaken in the clinic (ie, not at home).

1. End of Treatment/Withdrawal: visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
2. Palbociclib will be dosed QD from Day 1 through Day 21 of each cycle and should be taken approximately the same time in the morning with food.
3. ARV-471 dosing will begin on Cycle 1 Day 9. Drug will be dispensed to patients on Cycle 1 Day 8 to take home for dosing on subsequent days of Cycle 1. In Cycle 2 and beyond, ARV-471 dosing will begin on Day 1 with palbociclib. ARV-471 should be taken approximately the same time every day in the morning with food.
4. On Days 8 and 21, the patient will be provided a light meal after the pre-dose sample and prior to their palbociclib and/or ARV-471 dose in the clinic.
5. The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) should be obtained as closely as possible in succession, but no more than 2 minutes apart. All 12-lead ECGs should be confirmed by a qualified person at the institution and may be reviewed by a central laboratory. When coinciding with blood sample draws for PK, ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>60 msec increase from baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
6. Repeat as clinically indicated.
7. On Day 8, PK samples for palbociclib only will be collected.
8. For all PK sample collection, except for those on Cycle 1 Day 8, the PK sample collection is for both palbociclib and ARV-471. If the intensive PK collection on Cycle 1 Day 21 is not done, it can be postponed to Cycle 2 Day 15 after consulting with the sponsor.
9. The Day 15 (± 2) and Day 28 (± 2) PK collection only applies through Cycle 6.
10. The Day 15 (± 2) ECG collection only applies through Cycle 6.
11. A single timepoint assessment can be collected if the patient does not receive study treatment on this visit.

Table 7 Schedule for PK and ECG Assessments for Part B – Phase 2 Cohort Expansion

Note: No patients remain on study treatment in Part B as of Protocol Amendment 6.

Procedures	Screening (≤28 days prior to C1D1)	Study Treatment Period (PO, once daily) 1 Cycle (C)=28 days					End of Treatment/ Withdrawal ¹
		Cycle 1				Cycles 2 and beyond	
Visit Identifier (Visit Window)		Day 1	Day 2	Day 15 (±2)	Day 28 (±2)	Day 28 ² (±2)	
ARV-471		X	X	X	X	X	
Pharmacokinetics ³							
Pre-dose (if on dosing day)		X	X	X	X	X	X ⁶
Electrocardiogram ⁴							
Pre-dose (if on dosing day)	X	X		X	X	X	X ⁶
Echocardiogram ⁵	X						

Abbreviations: C=Cycle; D=Day; ECG=electrocardiogram; QTcF=corrected QT interval by Fridericia's method; PK=pharmacokinetics; PO=per oral. **Note:** On days of scheduled clinic visits, study drug treatment should be undertaken in the clinic (ie, not at home).

1. End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anti-tumor therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
2. Day 28 trough sample only (patient visit frequency reduced to every 28 days from every 2 weeks in the Part A – Phase 1 Dose Escalation).
3. For Part B, pre-dose trough samples will be taken on all patients.

4. The Screening ECG will be a single 12-lead ECG. At all other times, at each time point, 3 consecutive 12-lead ECGs (triplicate) should be obtained as closely as possible in succession, but no more than 2 minutes apart. All 12-lead ECGs should be confirmed by a qualified person at the institution and may be reviewed by a central laboratory. When coinciding with blood sample draws for PK, ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>60 msec increase from baseline or >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
5. Repeat as clinically indicated.
6. A single timepoint assessment can be collected if the patient does not receive study treatment on this visit.

Table 8 Schedule of Activities for Part A Patients who Have Been on Treatment Longer Than 6 Months (Have met Study Primary Completion Date)

Procedures ^{1, 2}	Study Treatment Period		Follow-Up (28-35 days) ⁵	Notes ⁶ There will be reduced recording of clinical data in the eCRF, but all data will continue to be recorded in the site source documents.
	Every 90-day cycles ³	EOT ⁴		
Treatment Day (Visit Window)	Day 1 (-14)		(+7)	
Hematology lab collection	X			Hematology lab collection should occur every 3 months or more frequently if clinically indicated and documented in site source but not collected by the Sponsor in the eCRF.
Chemistry lab collection	X			Chemistry lab collection should occur every 3 months or more frequently if clinically indicated and documented in site source but not collected by the Sponsor in the eCRF.
Pregnancy test and contraceptive check	X	X	X	Urine pregnancy tests will be done for WOCBP on treatment. Contraceptive check: see Section 8.1.6
ECG	X			ECGs should occur every 3 months or more frequently if clinically indicated and documented in site source but not collected by the Sponsor in the eCRF.
Manual ARV-471 drug dispensation	X			Refer to updated Pharmacy Manual.
ARV-471 administration	Once daily, oral			Refer to protocol Section 6.1 for administration instructions. Dosing diaries no longer need to be completed by the patient.
Compliance/accountability	X	X		Confirm and reconcile return of all bottles and remaining tablets of ARV-471. See protocol Section 6.3.1 .
AE and SAE monitoring	X ³	X	X	See Appendix 4 . AEs leading to discontinuation of study treatment and SAEs will continue to be collected on the eCRF; the SAE reporting process remains unchanged.
Concomitant treatments(s)	X	X	X	Collected in site source documents only (and on SAE form if applicable).

Procedures ^{1, 2}	Study Treatment Period		Follow-Up (28-35 days) ⁵	Notes ⁶ There will be reduced recording of clinical data in the eCRF, but all data will continue to be recorded in the site source documents.
	Every 90-day cycles ³	EOT ⁴		
EOT		X		End of Treatment eCRF to be completed to collect the reason for study drug discontinuation.
Collection of survival status ⁷		X	X	Survival Status eCRF to be completed at each survival visit, and End of Study eCRF to be completed at time of death, lost to follow-up, or withdrawal of consent. At time of death, Death Details eCRF should also be completed.

1. eCRF guidance in this table supersedes previous eCRF protocol guidance.
2. Standard of care clinical, laboratory, and imaging assessments: PE, weight, vital signs, ECOG, coagulation, and urinalysis can be assessed as clinically indicated per PI/site standard of care and documented in site source but will not be collected by the Sponsor in the eCRF. ctDNA samples should no longer be collected for study purposes. Tumor imaging (CT/MRI scans, bone scans) and tumor markers will be performed according to site standard of care and documented in site source, but not collected by the Sponsor in the eCRF.
3. AE monitoring should occur approximately every 30 days but can be completed by phone call per PI discretion. Patient can be seen more frequently as clinically indicated (eg, for AEs and/or suspicion of disease progression).
4. End of Treatment: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new antitumor therapy.
5. Follow-Up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, patients will return to undergo review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgement of the Investigator, that no further improvement is expected.
6. Changes described in Protocol Amendment 6 can be implemented at clinical sites once IRB approval is obtained.
7. Survival visits will occur every 3 months from EOT/Follow-up visit (whichever occurred later) until death, lost to follow-up, or withdrawal of consent. This visit may be performed by phone contact or office visit.

Table 9 Schedule of Activities for Part B Patients

Procedures ¹	Study Treatment Period	Notes
	Long-Term Follow-Up	
Collection of survival status ³	X	As of implementation of Protocol Amendment 6, this table is only applicable for Part B patients. ² Survival Status eCRF to be completed at each survival visit, and End of Study eCRF to be completed at time of death, lost to follow-up, or withdrawal of consent. At time of death, Death Details eCRF should also be completed.

1. eCRF guidance in this table supersedes previous eCRF protocol guidance.
2. Changes described in Protocol Amendment 6 can be implemented at clinical sites once IRB approval is obtained.
3. Survival visits will occur every 3 months from EOT/Follow-up visit (whichever occurred later) until death, lost to follow-up, or withdrawal of consent. This visit may be performed by phone contact or office visit.

Table 10 Schedule Of Activities for Part C Cohorts C1-C5 Patients who Have Been on Treatment Longer Than 6 Months (Have met Study Primary Completion Date)

Procedures ^{1, 2}	Study Treatment Period		Follow-Up (28-35 days) ⁵	Notes ⁶ There will be reduced recording of clinical data in the eCRF, but all data will continue to be recorded in the site source documents.
	Every 90-day cycles ³	EOT ⁴		
Treatment Day (Visit Window)	Day 1 (-14)		(+7)	
Hematology lab collection	See Notes			Hematology lab collection should occur monthly at the beginning of each cycle prior to treatment, or more frequently if clinically indicated and documented in site source but not collected by the Sponsor in the eCRF. Hematology labs can be done locally.
Chemistry lab collection	X			Chemistry lab collection should occur every 3 months or more frequently if clinically indicated and documented in site source but not collected by the Sponsor in the eCRF.
Pregnancy test and contraceptive check	X	X	X	Urine pregnancy tests will be done for WOCBP on treatment. Contraceptive check: see Section 8.1.6
ECG	X			ECGs should occur every 3 months or more frequently if clinically indicated and documented in site source but not collected by the Sponsor in eCRF.
Manual ARV-471 drug dispensation	X			Refer to updated Pharmacy Manual
Manual palbociclib drug dispensation	X			Refer to updated Pharmacy Manual
ARV-471 administration	Once daily, oral			Refer to protocol Section 6.1 for administration instructions. Dosing diaries no longer need to be completed by the patient.
Palbociclib administration	Once daily, oral (21D, 7D off)			Refer to protocol Section 6.1 for administration instructions. Palbociclib will be administered at the same time as ARV-471. Dosing diaries no longer need to be completed by the patient.
Compliance/accountability	X	X		Confirm and reconcile return of all bottles and remaining tablets of ARV-471 and capsules of palbociclib. See protocol Section 6.3.1 .

Procedures ^{1, 2}	Study Treatment Period		Follow-Up (28-35 days) ⁵	Notes ⁶ There will be reduced recording of clinical data in the eCRF, but all data will continue to be recorded in the site source documents.
	Every 90-day cycles ³	EOT ⁴		
AE and SAE monitoring	X ³	X	X	See Appendix 4 . AEs leading to discontinuation of study treatment and SAEs will continue to be collected on the eCRF; the SAE reporting process remains unchanged.
Concomitant treatments(s)	X	X	X	Collected in site source documents only (and on SAE form if applicable).
EOT		X		End of Treatment eCRF to be completed to collect the reason for study drug discontinuation.
Collection of survival status ⁷		X	X	Survival Status will only be collected for Cohorts C1-C4; it will not be collected for Cohort C5. Survival Status eCRF to be completed at each survival visit, and End of Study eCRF to be completed at time of death, lost to follow-up, or withdrawal of consent. At time of death, Death Details eCRF should also be completed.

1. eCRF guidance in this table supersedes previous eCRF protocol guidance.
2. Standard of care clinical, laboratory, and imaging assessments: PE, weight, vital signs, ECOG, coagulation, and urinalysis can be assessed as clinically indicated per PI/site standard of care and documented in site source but will not be collected by the Sponsor in the eCRF. ctDNA samples should no longer be collected for study purposes. Tumor imaging (CT/MRI scans, bone scans) and tumor markers will be performed according to site standard of care and documented in site source, but not collected by the Sponsor in the eCRF.
3. AE monitoring should occur approximately every 30 days but can be completed by phone call per PI discretion. Patient can be seen more frequently as clinically indicated (eg, for AEs and/or suspicion of disease progression).
4. End of Treatment: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of study drug and prior to initiation of any new anti-tumor therapy.
5. Follow-Up: At least 28 days, and no more than 35 days after discontinuation of study drug treatment, patients will return to undergo review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgement of the Investigator, that no further improvement is expected.
6. Changes described in Protocol Amendment 6 can be implemented at clinical sites once IRB approval is obtained.
7. Survival visits will occur every 3 months from EOT/Follow-up visit (whichever occurred later) until death, lost to follow-up, or withdrawal of consent. This visit may be performed by phone contact or office visit.

2. INTRODUCTION

2.1 Study Rationale

ARV-471 (PF-07850327) is a PROteolysis-Targeting Chimera (PROTAC[®]) small molecule that induces active degradation of the estrogen receptor (ER). ARV-471 is being developed for the treatment of patients with ER positive/human epidermal growth factor receptor 2 negative (ER+/HER2-) locally advanced or metastatic breast cancer (mBC). ARV-471 works by recruiting an E3 ligase to ubiquitinate ER which results in its subsequent degradation through the proteasome, a large, multi-subunit protein complex that degrades ubiquitinated proteins into small peptides. Such “active” degradation results in improved knockdown of tumor ER relative to fulvestrant in xenograft mouse models and produces tumor growth inhibition in vivo both as a single agent and in combination with palbociclib. Unlike fulvestrant, which is administered via intramuscular (IM) injections, ARV-471 is orally administered. Further, in early preclinical studies, ARV-471 has demonstrated greater ER degradation compared to other selective estrogen receptor downregulators (SERDs) in clinical development, such as AZD9496 and RAD1901 (Flanagan et al., 2017).

Fulvestrant, an ER-targeted agent, has become the cornerstone of endocrine regimens for patients with advanced disease. Fulvestrant works by destabilizing ER, causing the protein to be degraded. In preclinical models at doses which are not achievable in the clinic, fulvestrant only degrades 40-60% of ER, while ARV-471 degrades greater than 90% of ER, resulting in improved tumor growth inhibition (TGI). This improved TGI may translate into improved outcomes for patients whose disease has progressed on currently available therapies.

It should be noted that throughout this protocol, the abbreviation “ER” refers to estrogen receptor in general or to estrogen receptor alpha (ER α) since, in this therapeutic indication, the generic term ER is traditionally used, even though it is understood that breast cancers are generally ER α positive and in vitro diagnostic tests detect ER α . The beta form of estrogen receptor will be specifically identified as ER β .

Part C: Rationale:

Palbociclib

Cyclin-dependent kinases 4 and 6 (CDK4, CDK6), which are activated by D-type cyclins, promote cell cycle entry by phosphorylating retinoblastoma protein to initiate transition from the G1 phase to the S phase (Asghar et al., 2015). Several oncogenic signals in hormone receptor (HR)-positive breast cancer converge to promote expression of cyclin D1 and activation of CDK4 and CDK6 to drive breast cancer proliferation (Musgrove et al., 2011; Yu et al., 2006). In vitro evidence suggests that breast cancer that has developed resistance to prior endocrine therapy remains dependent on cyclin D1-CDK4 to promote proliferation (Miller et al., 2011; Thangavel et al., 2011).

CDK4/6 inhibitors are approved for use in combination with endocrine therapies as important standard of care options for patients with HR-positive advanced breast cancer. In comparison to

endocrine monotherapy, superior progression free survival (PFS) and overall survival (OS) has been achieved in patients treated with endocrine therapy (aromatase inhibitor or fulvestrant) in combination with a CDK4/6 inhibitor (palbociclib, abemaciclib, ribociclib) versus endocrine therapy alone.

Palbociclib (IBRANCE[®], Pfizer) was the first CDK4/6 inhibitor to be Food and Drug Administration (FDA)-approved, with indications for first-line therapy in combination with an aromatase inhibitor, and in endocrine therapy-resistant patients in combination with fulvestrant. Palbociclib is an orally active pyridopyrimidine, first-in-class compound that is a potent and highly selective reversible inhibitor of CDK 4/6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase.

Data from the PALOMA-3 Phase 3 study demonstrated that treatment with fulvestrant (intramuscular ER antagonist approved for the treatment of HR-positive, HER2-negative (HR+/HER2-) advanced or metastatic breast cancer in women with disease progression after endocrine therapy) in combination with palbociclib results in a clinically meaningful improvement in OS and PFS in comparison to fulvestrant/placebo ([Turner et al., 2018](#); [Cristofanilli et al., 2016](#)). The most common Grade 3 or 4 adverse events (AEs) in patients treated with the combination of palbociclib and fulvestrant were neutropenia, leukopenia, anemia, thrombocytopenia, and fatigue ([Turner et al., 2015](#)).

As described above, fulvestrant (FASLODEX[®], AstraZeneca) inhibits estrogen signaling through the ER primarily in 2 ways: competitive inhibition of estradiol binding to the ER, blocking nuclear localization, and accelerated degradation of the ER protein due to the instability of the fulvestrant-ER complex. Fulvestrant's destabilizing mechanism has validated the importance of ER degradation as a therapeutic approach. However, up to 50% of the ER can remain when compared to baseline levels after 6 months of fulvestrant treatment ([Agrawal et al., 2016](#)), indicating a need for more effective ER-degrading molecules.

In preclinical studies, the combination of ARV-471 and palbociclib resulted in significant tumor regression and anti-tumor activity when compared to palbociclib as a single agent or fulvestrant and palbociclib combination. In NOD/SCID mice harboring estradiol-stimulated MCF7 xenograft tumors, ARV-471 dosed orally daily at 30 mg/kg alone and in combination with palbociclib inhibited tumor growth (105% and 131%, respectively). ARV-471 decreased tumor ER α levels by >94% (Study ARV471-00009-00-INVIVO). Another study, in which ovariectomized female Nu/Nu mice harboring tamoxifen-resistant MCF7 cells were dosed orally daily with ARV-471 at 30 mg/kg alone and in combination with palbociclib, found tumor growth inhibited by 65% and 113%, respectively, and that the combination caused greater TGI when compared to the single-agent arms. ER α levels were decreased by approximately 72% in the tumors exposed to ARV-471 (Study ARV471-00011-00-INVIVO). These preclinical data suggest that ARV-471 has the potential to offer improved ER degradation and a more convenient route of administration as compared to fulvestrant either as monotherapy or in combination with palbociclib; the latter combination could potentially address a need in both first or later line therapy for advanced ER-positive (ER+) cancer.

2.2 Background

In the United States (US), breast cancer is the second leading cause of cancer death in women, with approximately 42,000 people expected to die from breast cancer in 2020 ([American Cancer Society, 2020](#)). While breast cancer is less common in men, men account for approximately 1% of all newly diagnosed cases, and almost 500 men are projected to die from their disease in 2020.

It is estimated that as of January 2017, approximately 155,000 women with mBC were living in the US. It was also reported that the number of women living with mBC is increasing primarily because of improvements in treatment and the aging of the US population. The estimated number of women living with mBC increased by 17% from 2000 to 2010 and is projected to increase by 31% from 2010 to 2020 ([Mariotto et al., 2017](#)).

Treatment options for advanced breast cancer or mBC depend on many different factors, including whether the tumors express hormone receptors (ER and/or progesterone receptor) or human epidermal growth factor receptor 2 (HER2). The standard of care for women with mBC is endocrine therapy, chemotherapy and/or targeted therapy alone or in combination. Patients with ER+ and HER2 negative (HER2-) mBC are treated with endocrine therapy, sometimes in combination with targeted drugs such as CDK4/6 inhibitors (CDKi). In patients with aggressive disease or whose disease continues to progress on endocrine therapy, chemotherapy may be prescribed.

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

Fulvestrant is considered the cornerstone component of ER-targeted endocrine regimens in the advanced disease setting, and works via an indirect mechanism of protein degradation, resulting in destabilization of ER. Single-agent fulvestrant is dosed at 500 mg IM QD on Days 1, 15, and 29 and once monthly thereafter. Efficacy of fulvestrant was established by comparison to the selective aromatase inhibitor anastrozole in 2 randomized, controlled clinical trials in postmenopausal women with locally advanced or mBC ([Astra Zeneca Faslodex Full Prescribing Information, revised 7/2020](#)). All patients had progressed after previous therapy with an antiestrogen or progestin for breast cancer in the adjuvant or advanced disease setting. In both trials, eligible patients with measurable and/or evaluable disease were randomized to receive either fulvestrant 250 mg IM QD once a month (28 days + 3 days) or anastrozole 1 mg orally once a day. Results of the trials, after a minimum follow-up duration of 14.6 months, ruled out inferiority of fulvestrant to anastrozole. There was no statistically significant difference in OS between the 2 treatment groups after a follow-up duration of 2 years or more. A third study compared fulvestrant 500 mg QD dose to fulvestrant 250 mg QD dose. Results of this study after a minimum follow-up duration of 18 months showed that PFS was statistically significantly

superior with fulvestrant 500 mg versus fulvestrant 250 mg (6.5 months versus 5.4 months, respectively). There was no statistically significant difference in OS between the 2 treatment groups (25.1 months for fulvestrant 500 mg and 22.8 months for fulvestrant 250 mg). Overall response rates (ORR) were similar; the response rate for the 500 mg dose was 13.8 % (95% CI 9.7-18.8%) and for the 250 mg dose was 14.6% (95% CI 10.5-19.4%) ([Astra Zeneca Faslodex Full Prescribing Information, revised 7/2020](#)).

2.3 Nonclinical Pharmacology

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 preclinical studies have been conducted to confirm the mechanism of action for ARV-471 and assess its in vitro anti-cancer effects in cell lines.

2.3.1 In Vitro Studies

A panel of ER+ cell lines were used to demonstrate ARV-471-based degradation of ER. A dose-dependent decrease in ER levels in 6 ER+ cell lines (MCF7, T47D, BT474, CAMA-1, ZR751, 134-VI) was observed. Moreover, the extent of ER loss by ARV-471 was similar to that seen with fulvestrant, which also targets ER. When immunofluorescence was used to measure ER levels as a function of ARV-471 concentrations in MCF7 cells, a half-maximal degradation concentration (DC₅₀) of 0.9 nM was achieved with maximum ER degradation of >90%. No degradation of ER was seen in MCF7 cells when excess cereblon ligand (lenalidomide) was included with ARV-471 or when a proteasome inhibitor (carfilzomib) was added. These observations support the proposed mode of action of ARV-471 in degrading ER via the proteasome by hijacking the intended intracellular E3 ligase.

In addition to ARV-471, its epimer ARV-473, was assessed for ER degradation activity. While both ARV-471 and fulvestrant reduced ER levels, ARV-473 did not reduce ER levels, even when tested at 10 μM. In an ER-dependent gene reporter assay, 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 (Investigator's Brochure).

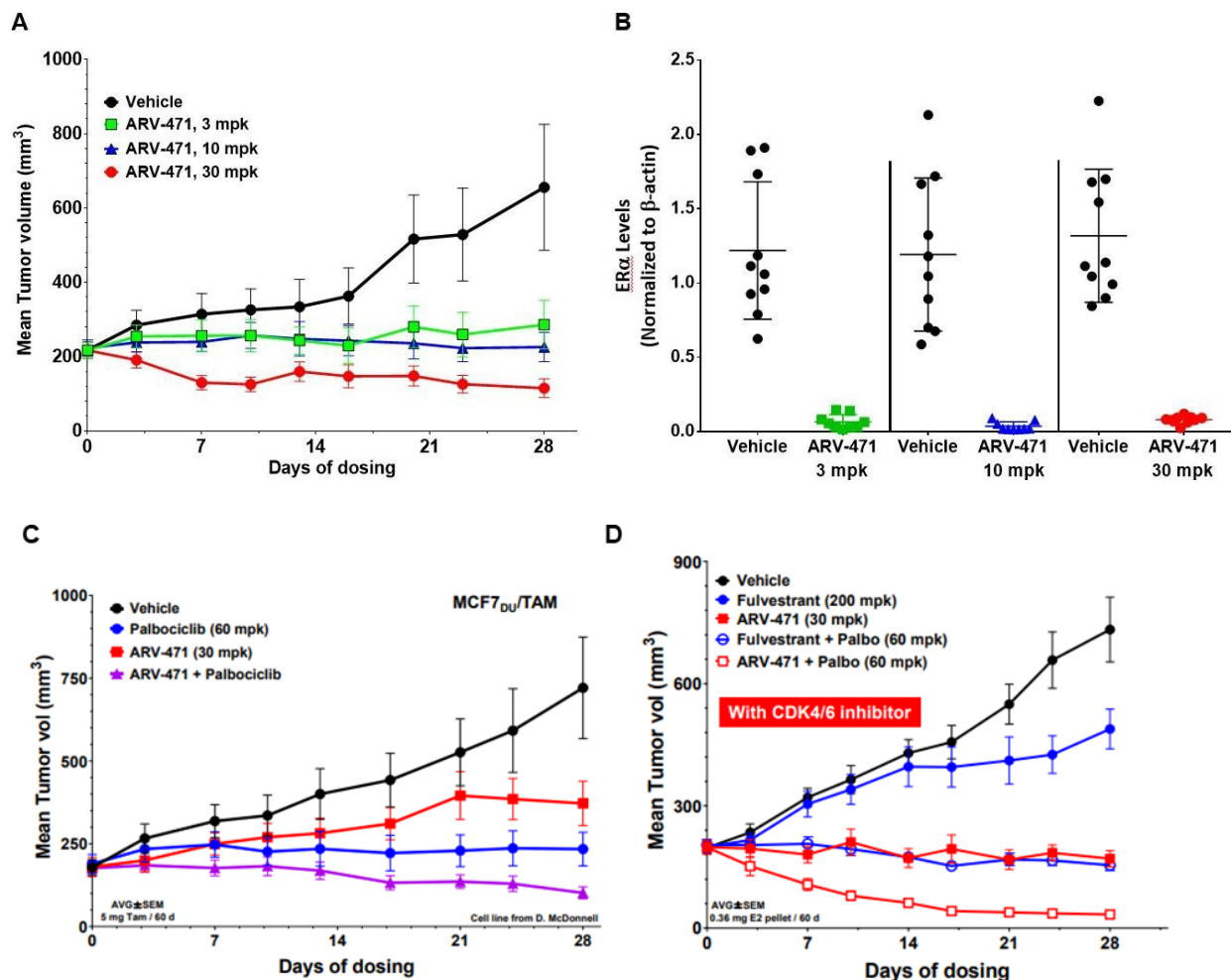
To characterize the functional consequences of ARV-471 binding to and degrading ER, cell proliferation experiments were conducted using 2 ER-dependent cell lines, MCF7 and T47D. ARV-471 caused a concentration-dependent decrease in proliferation in both cell lines tested with half-maximal growth inhibition (GI₅₀) values of 4 nM and 1.7 nM in MCF7 and T47D cells, respectively. For comparison, another anti-endocrine agent (and ER degrader), fulvestrant, provided a dose-dependent, anti-proliferative effect in both cell lines with GI₅₀ values <1 nM – which is consistent with previously published data ([Wakeling et al., 1991](#)).

One mechanism of acquired resistance to current endocrine therapies is the presence of constitutively activating mutations in the ER receptor 1 (ESR1) gene in metastatic ER+ breast cancer (Robinson et al., 2013) and (Toy et al., 2017). ARV-471 decreased levels of clinically relevant ER (Y537S) and ER mutant (D538G) proteins in a dose-dependent manner, similar to fulvestrant. In the same study, ARV-471 inhibited growth of these T47D cell lines with GI₅₀ values of 50 nM and 8 nM for ER (Y537S) and ER mutant (D538G), respectively. Taken together, ARV-471 demonstrates both ER degradation and anti-proliferative activity in cells expressing the most prevalent ESR1 mutations (Investigator's Brochure).

2.3.2 In Vivo Studies

To assess ARV-471 efficacy and ER degradation in vivo, ARV-471 was administered via oral gavage to MCF7-tumor-bearing mice. ARV-471 displayed dose-dependent efficacy (Figure 5A) with doses of 3 and 10 mg/kg/day inhibiting tumor growth by 85% and 98%, respectively, relative to vehicle and at 30 mg/kg/day, leading to tumor shrinkage (124% TGI). At study termination, the tumors were removed from the mice and ER levels were determined by immunoblotting the tumor homogenates. As seen in Figure 5B, ARV-471 at all doses significantly reduced ER levels by >94% when compared to mice administered vehicle only. Taken together, these data demonstrate that ARV-471 displays potent anti-tumor activity in a well-established in vivo ER+ breast cancer model, concurrent with robust degradation of ER in the tumors. These data establish that the minimum efficacious dose of single-agent ARV-471 in the MCF7/E2 xenograft model is 3 mg/kg (per oral [PO], once daily [QD]) (see Investigator's Brochure).

Figure 5 ARV-471 Significantly Inhibits Tumor Growth in a Dose-dependent Manner and Reduces ER Levels in the MCF7 Xenograft Model



Abbreviations: ER=estrogen receptor; ER α =estrogen receptor alpha; mpk=mg/kg; PO=per oral; QD=once daily; TGI=tumor growth inhibition.

(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 $\times$ 28; PO) was initiated once the tumors reached 200 mm³. 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. (C) In combination with 60 mg/kg palbociclib, 30 mg/kg ARV-471 achieves tumor regressions in a tamoxifen-resistant MCF7 xenograft that has become dependent on tamoxifen for growth (MCF7_{DU}/TAM). (D) Tumor regression (>80%) was achieved in all 10 mice treated with palbociclib + ARV-471 in a standard MCF7 xenograft model.

Source: Study No. ARV471-00009-00-INVIVO.

To evaluate the effects of combining ARV-471 with a CDK4/6 inhibitor, MCF7-tumor bearing mice were orally administered ARV-471 (30 mg/kg/day) and the CDK4/6 inhibitor palbociclib (60 mg/kg/day) for 28 days (Figure 5C-D). When compared to single-agent ARV-471 activity

(105% TGI) in this model, the combination of ARV-471 and palbociclib provided increased tumor regressions (131% TGI) (Investigator's Brochure).

2.3.3 Secondary Pharmacodynamics

ARV-471 (1 μ M) was assessed for binding to 86 receptors (including ER), ion channels, transporters, or other enzymes. Inhibition greater than 50% with ARV-471 was seen with 5 targets and was followed up with a concentration-response assay to determine half-maximal inhibitory concentration (IC_{50}) values to those identified targets and additionally to ER β , another estrogen-binding receptor sharing 55% homology to the ligand-binding domain of ER (Kuiper et al., 1996). ARV-471 demonstrated binding to ER (1 nM, IC_{50}), ER β (5 nM, IC_{50}), androgen receptor (AR; 100 nM, IC_{50}), glucocorticoid receptor (GR; 83 nM, IC_{50}), progesterone receptor (17 nM, IC_{50}), and opioid kappa receptor (250 nM, IC_{50}) (Investigator's Brochure).

As a follow-up to the biochemical binding results, no cellular degradation of AR and GR was observed after 72 hours with 1 μ M ARV-471. Degradation of progesterone receptor by ARV-471 was not evaluated as this receptor is an ER/estrogen-dependent gene product and thus antagonism/degradation of ER leads to decreased levels of progesterone receptor at the transcriptional level. The potential for ARV-471-mediated degradation of the opioid kappa receptor was not further studied, as this G protein-coupled receptor is primarily expressed in the brain (and prostate) (Uhlén et al., 2015), and ARV-471 has limited central nervous system (CNS) exposure (brain/plasma ratio <0.1) (Investigator's Brochure).

Given that ER β and ER α have homologous ligand-binding domains, many potent ER ligands display binding to both receptors, including currently approved drugs tamoxifen (Barkhem et al., 1998), raloxifene (Barkhem et al., 1998; Bryant et al., 1999) and fulvestrant. A concentration-dependent loss of ER β was seen with ARV-471 (DC_{50} ~1 nM) and to a lesser extent with fulvestrant, when these compounds were incubated on cells ectopically expressing epitope-tagged ER β (Investigator's Brochure).

Since ARV-471 engages the E3 ligase cereblon at the same binding site as immunomodulatory imide drugs (IMiDs) such as thalidomide, lenalidomide and pomalidomide, ARV-471 was evaluated for its degradation effect on known cereblon neomorphic substrates. In one study, overnight incubation of Ramos cells with increasing concentrations of ARV-471 did not lead to degradation of Ikaros, Aiolos, casein kinase 1 α (CK1 α), and G1 to S Phase Transition 1 gene (GSPT1), whereas the control IMiDs with known neomorphic substrate degradation activity (lenalidomide and CC-885) decreased levels of these neosubstrates. In another study with a cell line that expresses Sall4, a recently identified cereblon neomorphic substrate (Donovan et al., 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 μ M). 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 (Investigator's Brochure).

These preclinical data demonstrate that ARV-471, a potent, selective, orally bioavailable degrader of ER, effectively lowers ER levels in tumors, resulting in improved efficacy when compared to standard of care agent, fulvestrant.

2.4 Nonclinical Pharmacokinetics

The PK profile of ARV-471 in preclinical species (mouse, rat, dog, and monkey) was characterized by a low to moderate clearance (13.8 to 33.8% of hepatic blood flow), extensive tissue distribution (2.1 to 6.0 L/kg for volume of distribution at steady state), short to moderate terminal half-life of elimination ($T_{1/2}$) (2.1 to 8.2 hours), and moderate to good oral bioavailability (30 to 65%) (Investigator's Brochure).

After 6-day, QD, repeat doses of the 50-mg clinical tablet in chow-fed and fasted dogs, exposure was improved by 3-fold and inter-animal variability generally decreased among the fed animals. Little accumulation was observed over the course of the study. Bioavailability (%F) for the clinical tablets in chow-fed dogs was equivalent (%F ~40%) to that obtained for solution formulations administered at a similar dose. Based on these results, ARV-471 is recommended to be administered with food.

Dose-dependent increase in ARV-471 exposure was observed when ARV-471 was administered as an oral solution in the mouse (10, 30, 100 mg/kg), rat (30, 100, 300 mg/kg), dog (15, 45, 90 mg/kg), and monkey (1 and 3 mg/kg) (Investigator's Brochure).

In toxicokinetics, plasma exposure values (the maximum concentration, obtained directly from the observed concentration versus time data [C_{max}] and area under the plasma concentration-time curve to 24 hours [AUC_{0-24}]) were greater in females compared to males, by approximately 2-fold in dogs and generally greater than 2- to 3-fold in rats. The exposure (both C_{max} and AUC_{0-24}) consistently increased with dose, and the increase was dose proportional or slightly greater than dose proportional in both the rat and dog. In general, there was no evidence of accumulation after repeated dosing.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The extent of epimerization was limited (<15% based on the plasma ratio of formed epimer to dosed active pharmaceutical ingredient form) in the mouse, rat, and dog, and negligible in the monkey, when dosed with either ARV-471 or ARV-473. Additionally, the exposure of ARV-473 based on either C_{max} or AUC_{0-24} was <26% of those for ARV-471 in the rat or dog dose range finding or 28-day Good Laboratory Practice (GLP) toxicology studies of ARV-471 (Investigator's Brochure).

2.4.1 Absorption

Combined in vitro data suggests that ARV-471 is unlikely to be a substrate of intestinal efflux transporters including p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). A moderate to good extent of oral absorption was generally obtained when ARV-471 was dosed as a solution formulation in preclinical species, despite its low solubility and apparently low permeability in these in vitro assays (Investigator's Brochure).

Studies in fasted dogs and rats (ARV471-00051-00-INVIVO and ARV471-00054-00-INVIVO, respectively) showed a pH effect on absorption when administered with famotidine (lowered PK at neutral pH). However, these data do not characterize the fed conditions used in the clinical setting (Investigator's Brochure).

2.4.2 Distribution

ARV-471 plasma protein binding was moderately high across species, with the free fraction averaging 6.1% in the mouse, 8.2% in the rat, 2.6% in the dog, 4.0% in the monkey, and 12.4% in human at 1 μ M. The blood cell partitioning of ARV-471 in human blood at 5 μ M was limited with a blood cell/plasma concentration ratio of 0.18 (Investigator's Brochure).

Consistent with the large volume of distribution in the rat (volume of distribution [V_{ss}] of 6 L/kg), the tissue distribution of ARV-471 was extensive in the rat receiving once daily oral dose of ARV-471 at 100 mg/kg/day for 3 days. The tissue to plasma ratio ranged from ≤ 0.1 (brain) to 5.6 to 13.9 (lung). Tissue distribution data showed no signs of tissue accumulation upon repeat dose (Investigator's Brochure).

2.4.3 Metabolism

ARV-471 demonstrated relatively low turnover in liver microsomes and hepatocytes across species. Several metabolic pathways, including oxidation, dehydrogenation, dealkylation, sulfation, and glucuronidation, and a combination of oxidation and dealkylation, reduction, or methylation, were evident in liver microsomes and hepatocytes, along with hydrolysis in plasma, suggesting the involvement of both cytochrome P450 enzyme (CYP)-mediated and non-CYP-mediated metabolism in ARV-471 clearance. Products of *N*-dealkylation adjacent to the piperazine ring were the predominant metabolites detected. Several additional metabolic pathways including direct glucuronidation were observed in hepatocytes. No human unique metabolites were observed. Although it is not thought to be formed via enzymatic conversion, the epimer ARV-473 was found to circulate in both animal and human plasma. The clinical PK assessment will include both ARV-471 and ARV-473 (Investigator's Brochure).

2.4.4 Excretion

No experiments have been conducted to examine the excretion of ARV-471.

2.4.5 Pharmacokinetic Drug Interactions

Impact of CYP inhibitors/inducers on ARV-471

Study ARV-471-00063-00-INVITRO, a CYP reaction phenotyping study, was conducted consistent with current FDA guidance ([In Vitro Drug Interaction Studies, 2020](#)). This study indicated CYP3A4 as the principal isoform responsible for CYP metabolism of ARV-471 (accounting for 85%), while the contribution of CYP2C9 was shown to be minimal (4.3%). Based on these results, the potential for strong inhibitors and inducers of CYP2C9 to affect the PK of ARV-471 is expected to be minimal. 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 (Investigator's Brochure).

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

ARV-471 is an in vitro inhibitor of CYP2B6 with an IC_{50} of 16.0 μ M and may impact the exposure of sensitive substrates of CYP2B6 or CYP2B6 substrates with narrow therapeutic indices.

Nonclinical data indicate the potential of ARV-471 to inhibit human breast cancer resistance protein (BCRP). However, based on the clinical experience to date, patients enrolled in clinical trials will be allowed to receive sensitive BCRP substrates or BCRP substrates with narrow therapeutic indices. Supporting details are provided in the Investigator's Brochure.

Nonclinical data indicate the potential of ARV-471 to inhibit P-gp.

A summary of restrictions on concomitant medications is provided in Sections 5.1, 5.2, and 6.5.

Potential effects of palbociclib on ARV-471 PK

Palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, nor it is an inducer of CYP1A2, 2B6, 2C8, and 3A4. However, palbociclib is a weak, time-dependent inhibitor of CYP3A and has shown to increase the midazolam AUC_{INF} and the C_{max} values by 61% and 37%, respectively. Since ARV-471 is a CYP3A substrate, there is a potential for palbociclib to increase the exposure of ARV-471 when co-administered.

Palbociclib has low potential to inhibit P-gp, BCRP, OATP1B3, or OATP1B1 transporter. ARV-471 is unlikely to be a substrate for P-gp, BCRP, OATP1B1 and OATP1B3. The potential for palbociclib to affect the exposure of ARV-471 through these transporters pathways is considered low.

Potential effects of ARV-471 on palbociclib PK

ARV-471 does not inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6, or 3A4. ARV-471 inhibits CYP2B6. Palbociclib is a substrate of CYP3A and sulfotransferase (SULT) enzyme SULT2A1. Hence the potential for ARV-471 to affect the exposure of palbociclib through these metabolic pathways is considered low.

ARV-471 has shown no or minimal inhibition against OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K. In addition, ARV-471 is an inhibitor of P-gp and partially inhibits BCRP activity. Per the palbociclib USPI, P-gp and BCRP mediated transport are

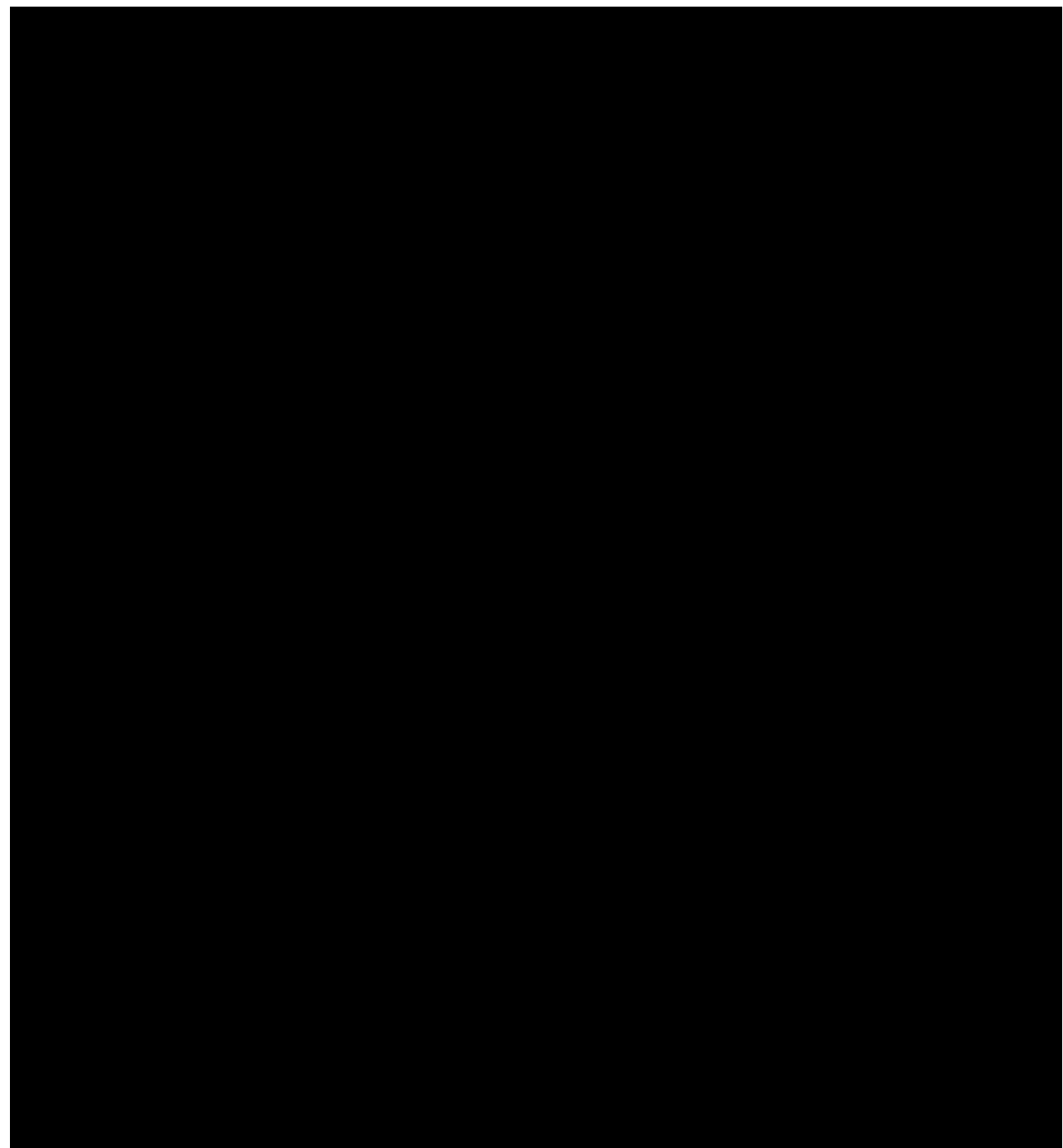
unlikely to affect the extent of oral absorption of palbociclib at therapeutic doses ([palbociclib USPI](#)). Hence, the potential for ARV-471 to affect the exposure of palbociclib through inhibition of P-gp or BCRP transporter pathways is considered low.

2.5 Nonclinical Toxicology

The 7- and 28-day oral toxicity studies in rats and dogs have consistently shown ARV-471 to be well tolerated after QD dosing. The studies have shown no clinical signs of toxicity following daily oral doses of ARV-471 up to 100 mg/kg/day in rats and 90 mg/kg/day in dogs, nor effects on overall health and well-being of the animals. 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]

In all toxicity studies, the notable effects of ARV-471 were on the reproductive systems of both female and male animals and showed recovery or evidence of reversibility following discontinuation of dosing. Reproductive tissues affected in the toxicology studies are known to bear both forms of the ER ([Nie et al., 2002](#)) and ([Martín de las Mulas et al., 2004](#)). Findings in the ovary (increased ovary weight, occurrence of cysts and corpus hemorrhagicum), uterus (atrophy) and cervix (atrophy) and, at low doses, asynchrony of estrous cycling (as seen in rats) are consistent with the pharmacological action of ARV-471 at the ER and have been observed for agents that target the ER (eg, fulvestrant) ([US FDA, 2002](#)). Findings in the testis, epididymis, and prostate are also consistent with effects seen in male animals dosed with ER inhibitors for at least 1 month ([US FDA, 2002](#)).

[REDACTED]



Taken together, the available nonclinical data support the initial clinical development of ARV-471, with NOAEL values being the highest dose levels in the studies: 100 mg/kg/day based on the 28-day toxicology study in female rats and 90 mg/kg/day based on the 28-day toxicology study in dogs.

2.6 Clinical Safety and Efficacy Overview

As of 13 April 2021, no DLTs have been reported with ARV-471 monotherapy among the 45 patients treated in dose-escalation and cohort expansion at doses up to 250 mg BID (500 mg total daily dose; N=6). In addition, 2 patients have received the 700-mg total daily dose for more than 28 days with no DLTs. The majority of treatment-related AEs are Grade 1 in severity, with treatment-related AEs in $\geq 10\%$ of patients limited to nausea, fatigue and arthralgia. Except for one patient in the 360-mg cohort who discontinued study treatment due to a Grade 3 thromboembolic event that was assessed as possibly related to treatment, there have been no additional Grade 3 treatment-related AEs or treatment discontinuations due to toxicity. In addition, ARV-471 demonstrates dose-related increase in PK through 500 mg dose level.

Although QT prolongation is not an expected AE based on nonclinical data (negative hERG assays and negative ECG studies conducted in dogs), as of 30 September 2021, 3 patients were reported to have QT prolongation. One patient treated at 180 mg had Grade 1 QTc prolongation that was considered unrelated to ARV-471 by the investigator; this event was reported as a TEAE, however, the QTc prolongation began prior to dosing on Cycle 1 Day 1 (C1D1). Two patients had QT prolongation considered by the investigator as related to ARV-471, and neither of the patients discontinued ARV-471 due to QT prolongation. One patient treated with a total daily dose of 500 mg had Grade 3 QTc prolongation that began around Cycle 1 Day 15, about 1 week after starting fluconazole 200 mg BID for the treatment of coccidiomycosis. This patient was on multiple medications known to prolong the QT interval (in addition to fluconazole). The second patient was treated at 120 mg, and had QTc prolongation around Cycle 1 Day 15. This patient was continued on ARV-471 without dose modification for several weeks after the event, and her QTc interval returned to near baseline values.

More detailed preliminary analyses performed as of a data cut-off of 28 Nov 2020 for the first 21 evaluable participants treated in the Part A monotherapy dose escalation suggest pharmacodynamic activity, and evidence of early clinical activity in a heavily pretreated population. Prior to enrollment, therapies received for advanced disease included CDK4/6 inhibitors (100% of patients); fulvestrant (71%), chemotherapy (38%), and investigational SERDs (24%). The 21 participants were treated across 5 dose levels: 30 mg QD (n=3), 60 mg QD (n=3), 120 mg QD (n=7), 180 mg QD (n=5), and 360 mg QD (n=3). Dose-related increases in exposure were observed. Doses ≥ 60 mg resulted in Cycle 1 Day 15 mean ARV-471 AUC₀₋₂₄ above the predicted efficacy thresholds (based on PK data from mice treated with 30 mg/kg).

Analysis of 5 paired tumor biopsies (1 at 30 mg QD, 1 at 60 mg QD, and 3 at 120 mg QD) demonstrated up to 90% ER degradation (average of 62%), including in 4 participants with an ESR mutation. Importantly, there was evidence of clinical benefit in this heavily treated population: the clinical benefit rate (CBR; proportion of patients with stable disease [SD] ≥ 24 weeks, or a best response of CR/PR) was 42% among 12 patients evaluable for CBR. This preliminary CBR based on a small sample size across multiple dose levels exceeds the estimated CBR of $<20\%$ for fulvestrant in the post CDK 4/6 setting (Juric et al., 2018, 2019).

Refer to the Investigator's Brochure for additional clinical information.

2.7 Benefit/Risk Assessment

ARV-471 may potentially benefit patients with locally advanced or mBC whose disease has progressed on currently approved standard of care agents. Preclinical and clinical data demonstrate that ARV-471, a potent, selective, orally bioavailable degrader of ER, effectively lowers ER levels in tumors, resulting in improved efficacy when compared to standard of care agent, fulvestrant. In addition, evidence of clinical benefit has been observed in this heavily treated population, with a 42% CBR among 12 evaluable patients.

As of 13 April 2021, no DLTs have been reported with ARV-471 monotherapy, and dose escalation continues at 700 mg QD. The majority of treatment-related AEs are Grade 1 in severity, with treatment-related AEs in $\geq 10\%$ of patients limited to nausea, fatigue and arthralgia. Except for one patient in the 360-mg cohort who discontinued treatment due to a Grade 3 thromboembolic event that was assessed as possibly related to treatment, there have been no additional Grade 3 treatment-related AEs or treatment discontinuation due to toxicity.

Preclinical toxicology studies performed in rats and dogs with ARV-471 using QD oral administration showed it was well tolerated in both 7- and 28-day studies. Based on the studies, potential adverse effects may include changes consistent with the pharmacologic activity of ARV-471 as an ER degrader, and similar to effects observed with other agents that target ER (eg, fulvestrant) when administered in healthy animals. These included reversible changes in the female reproductive tissues such as increased ovary weight and occurrence of ovarian cysts and corpus hemorrhagicum, and uterine and cervical atrophy. Findings in the testis, epididymis, and prostate of male animals were consistent with effects seen in male animals dosed with ER inhibitors for at least 1 month and also showed signs of reversibility. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Overall, it is not expected that the findings listed above should impact clinical studies with ARV-471 for the treatment of ER+/HER2- patients with locally advanced or mBC.

Additional potential adverse effects of ARV-471 may be similar to those observed with ER-degrading agents such as fulvestrant, and include nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. The most common laboratory abnormalities with fulvestrant were increased hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]) ([Astra Zeneca Faslodex Full Prescribing Information, revised 7/2020](#)).

Precautions will be taken to avoid these risks. Patients will be monitored closely throughout study participation (see [Section 8.1](#) for information regarding safety assessments). The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

ARV-471 and Palbociclib

In preclinical studies, the combination of ARV-471 and palbociclib resulted in significant tumor regression and anti-tumor activity when compared to palbociclib as a single agent or fulvestrant and palbociclib combination. In NOD/SCID mice harboring estradiol-stimulated MCF7 xenograft tumors, ARV-471 dosed orally daily at 30 mg/kg alone and in combination with palbociclib inhibited tumor growth (105% and 131%, respectively). ARV-471 decreased tumor ER α levels by >94% (Study ARV471-00009-00-INVIVO). Another study, in which ovariectomized female Nu/Nu mice harboring tamoxifen-resistant MCF7 cells were dosed orally daily with ARV-471 at 30 mg/kg alone and in combination with palbociclib, found tumor growth inhibited by 65% and 113%, respectively, and that the combination caused greater TGI when compared to the single-agent arms. ER α levels were decreased by approximately 72% in the tumors exposed to ARV-471 (Study ARV471-00011-00-INVIVO). These preclinical data suggest that ARV-471 has the potential to offer improved ER degradation and a more convenient route of administration as compared to fulvestrant either as monotherapy or in combination with palbociclib; the latter combination could potentially address a need in both first or later line therapy for advanced ER+ cancer.

As of 13 April 2021, no DLTs have been reported with ARV-471 monotherapy among the 45 patients treated in dose-escalation and cohort expansion at doses up to 250 mg BID (500 mg total daily dose). Palbociclib safety profile is primarily related to hematologic toxicity and more specifically neutropenia (see IBRANCE[®] USPI for palbociclib efficacy and safety data). No hematologic AEs have been reported for ARV-471 to date. These clinical data indicate there is unlikely to be a clinical overlap in toxicity between the 2 agents.

More detailed information about ARV-471 is provided in the ARV-471 Investigator's Brochure.

As of 01 November 2022, the safety profile of the combination of ARV-471 200 mg and palbociclib 125 mg was generally consistent with that observed after treatment with ARV-471 monotherapy (Study ARV-471-mBC-101 Part A dose escalation and Part B dose expansion), except for an increase in reported neutropenia (Data on File). The neutropenia was medically manageable, tolerable, and mostly asymptomatic in these patients. In the heavily pretreated patients from Part C, compared with historical data, there was an observed increase in palbociclib exposure in patients treated with ARV-471 in combination with palbociclib 125 mg. Cohort C5 is included to gain more understanding of the impact of ARV-471 on the clinical PK and safety of palbociclib 100 mg when given in combination with ARV-471.

3. OBJECTIVES AND ENDPOINTS

Table 11 Part A – Phase 1 Dose Escalation Study Objectives and Endpoints

Part A – Phase 1 Dose Escalation	
Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of ARV-471 in successive cohorts of patients in order to estimate the maximum tolerated dose and select the RP2Ds	The following safety endpoints will be assessed: • First cycle dose-limiting toxicities • Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
Secondary	
To characterize the single dose and steady-state PK of ARV-471 and ARV-473	The following PK parameters will be assessed when applicable after a single dose and after multiple doses: AUC_{0-tau}, AUC_{0-last}, C_{max}, C_{min}, CL/F, T_{max}, Vd/F, and accumulation ratios, Effective T_{1/2}, MRC_{max}, and MRAUC_{0-tau} (see Table 21 for definitions)
To explore preliminary anti-tumor activity	Anti-tumor activity of ARV-471 will be assessed by evaluating the following: • ORR per RECIST 1.1 • CBR based on the summation of CRs, PRs and stable disease of 24 weeks duration or longer • DCR (complete response, partial response, stable disease) • Time to event endpoints: PFS, DOR
Exploratory	
To characterize baseline ESR1 mutational status, which is a potential mechanism of resistance to prior ER-targeted therapies, and relevant molecularly defined subsets of patients	ESR1 mutational status in ctDNA and/or tumor tissue
To assess pharmacodynamic effects of ARV-471 on exploratory biomarkers	ER, progesterone receptor, and Ki-67 protein levels in pre- and post-treatment tumor biopsies in patients with accessible tumor tissue

Abbreviations: AUC_{0-last}=area under the plasma concentration-time curve from time zero to time of last measurable concentration; AUC_{0-tau}=area under the plasma concentration-time curve during a dosing interval, calculated by linear up/log down trapezoidal summation; CBR=clinical benefit rate; CL/F=apparent oral plasma clearance; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; CR=complete response; ctDNA=circulating tumor deoxyribonucleic acid; DCR=disease control rate; DOR=duration of response; Effective T_{1/2}=Effective half-life based on accumulation ratio; ER=estrogen receptor; ESR1=estrogen receptor 1;

MRAUC_{0-tau}=ARV-473 to ARV-471 ratio for AUC_{0-tau}; MRC_{max}=ARV-473 to ARV-471 ratio for C_{max}; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=overall response rate; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; RP2D=recommended Phase 2 dose; T_{max}=time to C_{max}; Vd/F=apparent volume of distribution after non-intravenous administration.

Note: ORR, CBR, DCR, DOR and PFS will be evaluated using RECIST 1.1.

Table 12 Part B – Phase 2 Cohort Expansion Study Objectives and Endpoints

Part B – Phase 2 Cohort Expansion	
Objectives	Endpoints
Primary	
To evaluate the anti-tumor activity of ARV-471 in patients with locally advanced or mBC	The anti-tumor activity of ARV-471 will be assessed by evaluating the following: • CBR based on the summation of CRs, PRs and stable disease of 24 weeks duration or longer
Secondary	
To further evaluate the anti-tumor activity of ARV-471 in patients with locally advanced or mBC	Anti-tumor activity of ARV-471 will be assessed by evaluating the following: • ORR per RECIST 1.1 in patients with measurable disease at baseline • DOR • PFS • OS
To further evaluate the safety and tolerability of ARV-471 in patients with locally advanced or mBC	• Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
To determine plasma concentrations of ARV-471 and ARV-473	Pre-dose concentrations of ARV-471 and ARV-473
Exploratory	
To characterize baseline ESR1 mutational status, which is a potential mechanism of resistance to prior ER-targeted therapies, and relevant molecularly defined subsets of patients	ESR1 mutational status in ctDNA and/or tumor tissue

To assess pharmacodynamic biomarkers of ARV-471	ER, progesterone receptor, and Ki-67 protein levels in pre- and post-treatment tumor biopsies in patients with accessible tumor tissue
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Abbreviations: CBR=clinical benefit rate; CR=complete response; ctDNA=circulating tumor deoxyribonucleic acid; DOR=duration of response; ER=estrogen receptor; ESR1=estrogen receptor 1; mBC=metastatic breast cancer; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=overall response rate; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1.

Note: CBR, ORR, DOR, and PFS will be evaluated using RECIST 1.1.

Table 13 Part C – Combination ARV-471 + Palbociclib Study Objectives and Endpoints

Part C – Combination ARV-471 + Palbociclib	
Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of ARV-471 in combination with palbociclib and select the recommended Phase 2 dose/schedule for the combination	The following safety endpoints will be assessed: - First-cycle DLTs and determination of an MTD, if applicable, among the doses evaluated - Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug combination - Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
Secondary	
To characterize the first dose and steady-state PK of ARV-471, ARV-473, and palbociclib when ARV-471 is administered in combination with palbociclib	The following PK parameters will be assessed for ARV-471, ARV-473, and palbociclib when applicable after a single dose and after multiple doses: AUC _{0-tau} , AUC _{0-last} , C _{max} , C _{min} , CL/F, T _{max} , Vd/F, and accumulation ratios, Effective T _{1/2} , MRC _{max} , and MRAUC _{0-tau} (see Table 21 for definitions)
To characterize the steady state PK of palbociclib when given alone and in combination with ARV-471 in Part C Cohort C5.	PK parameters of palbociclib AUC _{0-tau} , and C _{max} , and other PK parameters if data permits (T _{max} , CL/F, Vd/F, etc)
To assess preliminary anti-tumor activity of ARV-471 in combination with palbociclib	Anti-tumor activity of ARV-471 in combination with palbociclib will be assessed by evaluating the following: - ORR per RECIST 1.1 in patients with measurable disease at baseline - CBR based on the summation of CRs, PRs and stable disease of 24 weeks duration or longer - Time to event endpoints: PFS, DOR, OS

Exploratory	
To characterize tumor mutational status, including ESR1, which is a potential mechanism of resistance to prior ER-targeted therapies	Determine the mutational status of ESR1 and other genes related to ER signaling in ctDNA and/or tumor tissue
To assess pharmacodynamic effects of ARV-471 on exploratory biomarkers	ER, progesterone receptor, and Ki-67 protein levels in pre- and post-treatment tumor biopsies in patients with accessible tumor tissue

Abbreviations: AUC_{0-last} =area under the plasma concentration-time curve from time zero to time of last measurable concentration; AUC_{0-tau} =area under the plasma concentration-time curve during a dosing interval, calculated by linear up/log down trapezoidal summation; CL/F =apparent oral plasma clearance; C_{max} =maximum plasma concentration; C_{min} =minimum plasma concentration; ctDNA=circulating tumor deoxyribonucleic acid; DLT=dose-limiting toxicity; Effective $T_{1/2}$ =Effective half-life based on accumulation ratio; ER=estrogen receptor; ESR1=estrogen receptor 1; MTD=maximum tolerated dose; $MRAUC_{0-tau}$ =ARV-473 to ARV-471 ratio for AUC_{0-tau} ; MRC_{max} =ARV-473 to ARV-471 ratio for C_{max} ; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PFS=progression-free survival; PK=pharmacokinetics; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; T_{max} =time to C_{max} ; Vd/F =apparent volume of distribution after nonintravenous administration.

Note: ORR, CBR, DOR, and PFS will be evaluated using RECIST 1.1.

4. STUDY DESIGN

4.1 Overall Design

This study is designed as a 3-part, first-in-human, open label, sequential group study including a Phase 1/2, 3+3 dose escalation and cohort expansion of single agent ARV-471, and a Phase 1b investigation of ARV-471 in combination with palbociclib.

This study will assess the safety and tolerability, and determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D), of ARV-471, either as a single agent or in combination with palbociclib, in patients with locally advanced or mBC. The study will also assess clinical activity of ARV-471 at the RP2Ds for monotherapy and in combination with palbociclib. Additional evaluation will include single- and multiple-dose pharmacokinetics and biochemical activity.

Study Phase

Part A: Phase 1

Part B: Phase 2

Part C: Phase 1b

See [Figure 4](#) for the Overall Study Schema.

Part A – Phase 1 Dose Escalation: The Part A – Phase 1 Dose Escalation aims to determine the MTD and/or RP2Ds of ARV-471 as monotherapy. ARV-471 will be administered orally QD or twice daily (BID), and dose escalation will follow a standard 3+3 design (as described below under [Dose Escalation](#)). The first cohort will be Cohort 1 and subsequent cohorts will be Cohort 2, Cohort 3, etc.

Additional patients (up to 20 total per dose level) may be added to previously studied dose-escalation cohorts once the CRC has deemed the dose to be safe. These additional patients will allow for further characterization of the safety of ARV-471 as well as its PK/pharmacodynamics profile.

At the discretion of the Principal Investigator, intra-patient dose escalation is permitted if the next higher dose level has been declared safe by the CRC and if the patient has had no Grade 2 or greater toxicities deemed related to study drug. All such requests must be reviewed and approved by the Sponsor's Medical Monitor.

Patients will be monitored for treatment-emergent adverse events (TEAEs) and DLTs.

Dose-escalation rules during the study are based on both the severity and frequency of any safety signals as defined in the protocol ([Section 4.4](#)). Patients may remain on study beyond Cycle 1 at the discretion of the Principal Investigator, until disease progression*, unacceptable toxicity, or withdrawal of consent. Patients in this Phase 1/2 study will not be pre-selected based on ER gene mutational status, however, mutational status will be retrospectively analyzed. See [Section 4.4.1](#) for details regarding criteria for dose escalation. Definitions for DLT, MTD, optimal biological dose, and RP2D are presented in [Appendix 5](#).

*Patients who have evidence of radiographic disease progression may be considered for continued study drug treatment provided the Principal Investigator has determined that they are still benefiting from study drug. All such requests must be reviewed and approved by the Sponsor's Medical Monitor.

The Part B – Phase 2 Cohort Expansion: Part B aims to assess the activity of the recommended doses of ARV-471 monotherapy in a population of patients who have previously received a CDK4/6 inhibitor and experienced progression on endocrine therapy in the advanced/metastatic setting, but have received no more than 1 prior chemotherapy regimen. In Cohort B1, approximately 30 patients will receive ARV-471 as monotherapy at 200 mg QD. In Cohort B2, approximately 30 patients will receive ARV-471 as monotherapy at 500 mg QD. If both cohorts are open to accrual simultaneously, sequential patients will be enrolled to each cohort in an alternating fashion.

Part C – Combination ARV-471 + Palbociclib (Cohorts C1-C4): Part C aims to determine the safety and recommended dose of ARV-471 in combination with palbociclib. ARV-471 will be administered orally QD, and palbociclib will be administered according to the approved palbociclib (IBRANCE®) USPI.

Part C will include 2 dose-escalation levels for ARV-471 in combination with palbociclib prior to the expansion cohorts: 1) 200 mg QD (Cohort C1; initially 180 mg QD but rounded up to 200 mg QD upon availability of the 100-mg tablets), and 2) 400 mg QD (Cohort C2). The CRC

will review the safety data of each cohort and recommend escalation or not. If Cohort C1 and C2 are approved for escalation, expansion at the dose of 500 mg ARV-471 with palbociclib (Cohort C3) and 200 mg ARV-471 with palbociclib (Cohort C4) will begin. If an intermediate dose for combination is recommended by the CRC based on the 2 dose-escalation Cohorts C1 and C2, then the expansion cohort C3 will use that recommended dose in combination with palbociclib. Cohorts C1 and C2 will consist of 3-6 patients each, followed by approximately 20 patients each enrolled in Cohorts C3 and C4. If Cohorts C3 and C4 are open to accrual simultaneously, sequential patients may be enrolled to each cohort in an alternating fashion.

Part C - Combination ARV-471 + Palbociclib (Cohort C5 ONLY):

Part C also includes Cohort C5, which aims to evaluate the safety of treatment with palbociclib 100 mg QD (21 days on followed by 7 days off treatment) and ARV-471 200 mg QD and to further evaluate the steady state PK of palbociclib in the absence and presence of ARV-471 200 mg. In Cycle 1, palbociclib 100 mg will be given alone for 8 days (C1D1 through C1D8), prior to starting ARV-471 200 mg QD on Cycle 1 Day 9. Palbociclib 100 mg QD will begin on C1D1 and be given for 21 days followed by 7 days off treatment ([Figure 1](#)). In Cycles 2 and beyond, patients will receive, starting on Day 1, ARV-471 200 mg QD continuously and palbociclib 100 mg QD for 21 days followed by 7 days off-treatment.

The SRC will then continue to monitor safety throughout Part C for patients receiving ARV-471 in combination with palbociclib until all patients have completed study drug treatment or final database lock occurs.

All phases of this study consist of the following periods:

Screening Period: Patients are evaluated for eligibility and consented to participate in the study.

Study Treatment Period: After verification of eligibility, patients will enter the treatment phase and will receive ARV-471 as monotherapy (Part A and B) or in combination with palbociclib (Part C), in 28-day cycles. Study visits for evaluation of safety (ie, AEs, physical exam [PE], vital signs, laboratory assessments) will occur weekly during the first cycle and biweekly thereafter for patients in Part A and Part C, and biweekly during the first cycle and monthly thereafter for patients in Part B.

Radiographic imaging for assessment of disease status will be performed every 8 weeks.

All patients may continue treatment at the discretion of the Principal Investigator until a treatment discontinuation criterion is met (see [Section 7.1](#)). Patients who have evidence of radiographic disease progression may be considered for continued study therapy provided the Principal Investigator has determined that they are still benefiting from study therapy. All such requests must be reviewed and approved by the Sponsor's Medical Monitor.

End of Treatment and Follow-up Period:

The End of Treatment (EOT) visit is to be performed as soon as possible, but no later than 4 weeks from the last dose of study drug and prior to initiation of any new anti-tumor therapy. Assessments should be obtained if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments). Laboratory

assessments and PEs will be performed at the EOT Visit. AEs will be collected, and information will be recorded in the AE electronic case report form (eCRF) page.

Any TEAEs that are ongoing will be assessed at the Follow-up visit that will take place 28 to 35 days after treatment discontinuation. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

Survival visits will occur every 3 months from EOT/Follow-up visit (whichever occurred later) until death, lost to follow-up, or withdrawal of consent, as outlined in the SoA ([Section 1.3](#)). This visit may be performed by phone contact or office visit.

Please see [Table 8](#), [Table 9](#), and [Table 10](#) for reduced EOT assessments as of Protocol Amendment 6.

4.2 Scientific Rationale for Study Design

The purpose of this first-in-human clinical study is to assess the safety and tolerability of ARV-471 as a single agent and in combination with palbociclib in patients with ER+/HER2- locally advanced or mBC. The study will also determine the single dose and steady state PK profiles of ARV-471, ARV-473, and palbociclib when ARV-471 is administered in combination with palbociclib (in Part C), and assess preliminary biochemical and clinical activity of ARV-471 in this population.

The Part A – Phase 1 Dose Escalation is a conventional 3+3, open label, multicenter study design. Ultimately, data from Part A will determine the RP2D for ARV-471. The evaluation will also provide an initial description of AEs associated with ARV-471 administration in a dose-dependent fashion. A target toxicity rate of $\leq 33\%$ has traditionally been considered acceptable in the oncology field. The 3+3 design will allow for a sufficient number of treated patients to assess safety and minimize the number of patients treated at doses that are not expected to produce patient benefit.

The Part B – Phase 2 Cohort Expansion will allow for further characterization of the safety and efficacy of ARV-471 at the RP2Ds as well as its PK/PD. The multi-center approach will increase efficiency in the conduct of the study.

The Part C– Phase 1b Combination will allow for characterization of the safety and preliminary efficacy of ARV-471 in combination with palbociclib as well as its PK/PD. The multi-center approach will increase efficiency in the conduct of the study.

4.3 Justification for Dose, Route of Administration, and Dosing Schedule

Route of Administration for ARV-471

Patients will receive ARV-471 orally either QD or BID with food (eg, a light meal of approximately 400 to 600 calories which includes a mixture of fat, carbohydrates, and protein).

Rationale for Administration of ARV-471 with Food

In a 6-day, QD, repeat-dose study of the ARV-471 50 mg clinical tablet in chow-fed and fasted dogs, exposure was improved 3-fold and inter-animal variability generally decreased among the fed animals. Little accumulation was observed over the course of the study.

As a result, it is planned that ARV-471 will be administered to patients with food in the initial patient study.

Bioavailability for the clinical tablets in chow-fed, pentagastrin-pretreated dogs was equivalent (%F ~40%) to that obtained for solution formulations administered at a similar dose.

4.3.1 Starting Dose – Part A – Phase 1 Dose Escalation

The starting dose for patients in the initial clinical study was 30 mg, taken orally QD with food. The 30-mg dose has been selected based on consideration of evidence of both pharmacology-related effects and toxicology results for ARV-471 in studies in rats and dogs, and consideration of FDA's guidance on the calculation of maximum starting doses in clinical trials ([US FDA, 2005](#)) and the International Council for Harmonization (ICH) S9 guidance for anti-cancer drugs ([ICH, 2009](#)). Additional PK data from a tablet study in dogs are available to support the use of the tablet administered with food in the clinic (see [Section 2.4](#)).

Considerations Based on Nonclinical Toxicology Information

Consideration was also given to a safe starting dose for ARV-471 based on the NOAEL values determined in the GLP toxicology studies in rats and dogs ([US FDA, 2002](#)). The rat NOAEL value of 100 mg/kg/day yields a maximum safe starting dose of 96.8 mg/day for a 60-kg adult following conversion of the rat NOAEL to the human equivalent dose (HED) and the inclusion of a 10-fold safety factor. Compared to a calculation of a maximum safe human starting dose based on the NOAEL from the study in dogs (ie, 300 mg/day), the rat study NOAEL provides a more conservative approach for a maximum safe starting dose in humans when based on nonclinical toxicology information.

Given that the mechanism of action of ARV-471 is novel, the calculation of a safe starting dose in humans based on a NOAEL is considered to be more conservative and appropriate than the approach recommended for cytotoxic anti-cancer agents, which is based on either a severely toxic dose in 10% of rodents (STD10) or on a highest non-severely toxic dose in nonrodents. It is acknowledged that as there was no severe toxicity in the rat study, the STD10 would effectively have been the same as the study-high dose of 100 mg/kg/day, which was the NOAEL for daily dosing in rats.

Estimated Human Efficacious Dose Projection

Based on consideration of the available in vivo mouse activity data for ARV-471, the human dose needed to achieve minimally efficacious exposure is predicted to fall in the range from 14 to 38 mg QD for a 60-kg adult (ie, equivalent to 28 to 76 mg QD, based on total drug). This prediction was based on the lowest efficacious dose in the NOD/SCID mouse model (3 mg/kg) and the plasma exposure levels observed in the model.

Summary of Human Starting Dose Determination

In summary, the starting dose of 30 mg taken orally QD with food is the recommended starting dose in the initial clinical trial for ARV-471 in patients with ER+/HER2- locally advanced or mBC. This calculated starting dose level of 30 mg QD is based on the pharmacology-related effects seen at the lowest dose tested in the 28-day toxicology study in rats and is within the predicted human minimally efficacious dose range. This starting dose is considered to be conservative since it is significantly lower than the starting dose based on the NOAEL values determined in the GLP toxicology studies.

4.3.2 Part B – Phase 2 Cohort Expansion

Two doses have been selected for evaluation in Part B; 200 mg QD (Cohort B1) and 500 mg QD (Cohort B2).

Cohort B1:

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

- No DLT or treatment-related serious adverse events (SAEs) had occurred at doses up to and including 180 mg QD
- One treatment related SAE occurred at the 360 mg QD dose level, a Grade 3 thromboembolic event. No DLT, additional treatment-related SAE or Grade 3/4 treatment-related events had been reported among the 13 patients who had completed at least 1 cycle of ARV-471 at 360 mg QD.
- The majority of reported AEs had been Grade 1. Grade 2 treatment-related AEs had been reported at doses of 120 mg and higher. The only Grade 2 treatment-related AE to occur in more than 1 patient was nausea (n=2).
- Preliminary PK, PD and efficacy data from the first 20 patients treated at doses up to 360 mg QD, shared by ARVINAS via webcast presentation on 14 Dec 2020, were as follows:
 - ARV-471 demonstrates dose-related increase in PK, with doses of 60 mg QD and above resulting in exposures that far exceed the efficacious threshold for tumor regression in preclinical models.
 - Based on data from the first 3 dose levels (30-120 mg), significant ER degradation (up to 90% with an average of 62%) was observed in patient tumor biopsies, which exceeds the 40-50% degradation reported for fulvestrant. Degradation of both wild-type ER and ESR1-mutant proteins was observed. ([Robertson et al., 2013](#); [Kuter et al., 2012](#))

- A confirmed PR (with 51% shrinkage in tumor burden) was observed in a patient who received ARV-471 at 120 mg QD, and who was heavily pretreated with multiple lines of endocrine therapy and prior CDK4/6.
- Shrinkage of measurable lesions was observed in 71% (10/14) of evaluable patients, and occurred across multiple dose levels.
- The CBR (defined as SD persisting ≥ 24 weeks, or a best response of confirmed CR or PR) was 42% (5/12) among evaluable patients up to 180 mg, which exceeds the CBR ($< 20\%$) reported for fulvestrant in a similar population. Clinical benefit was also observed across dose levels.

The ARV-471-mBC-101 CRC and Arvinas agreed that, taken together, these data supported initiation of Part B with the 200-mg QD ARV-471 dose (representing a rounding up from 180 mg QD to accommodate the 100-mg tablets).

Cohort B2:

As of 13 April 2021, the dose escalation has proceeded through 30 mg QD, 60 mg QD, 120 mg QD, 180 mg QD, 360 mg QD, 500 mg total daily dose (administered initially as a 250-mg BID dose, transitioned to QD dosing upon availability of 100-mg tablets), and 700-mg total daily dose level (administered initially as 400/300 BID dosing, transitioned to QD dosing upon availability of 100 mg tablets). Data that support the selection of 500 mg QD for evaluation in Cohort B2 are as follows:

- No DLTs have been reported with ARV-471 monotherapy among the 45 patients treated in dose escalation and cohort expansion at doses up to 250 mg BID (500-mg total daily dose). In addition, 2 patients have received the 700-mg total daily dose for more than 28 days with no DLT.
- The majority of treatment-related AEs are Grade 1 in severity, with treatment-related AEs in $\geq 10\%$ of patients limited to nausea, fatigue and arthralgia.
- Except for 1 patient in the 360-mg cohort who discontinued study treatment due to a Grade 3 thromboembolic event that was assessed as possibly related to treatment, there have been no additional Grade 3 treatment-related AEs or treatment discontinuations due to toxicity.
- Dose-related increase in PK through 500-mg dose level.
- The NOAEL in nonclinical toxicology studies (female rat) was 100 mg/kg/day, which is equivalent to a human dose of approximately 960 mg. Refer to the Investigator's Brochure for details.
- ARV-471 efficacy in patient-derived xenograft models was dose proportional.

4.3.3 Part C – Combination of ARV-471 + Palbociclib Dose Justification

The starting dose for ARV-471, when given in combination with palbociclib, was determined to be 180 mg QD based on safety data available as of 06 Oct 2020. At that time, 23 patients had been treated across 4 dose levels (N=3 at 30 mg, N=3 at 60 mg, N=7 at 120 mg, N=7 at 180 mg

and N=3 at 360 mg). Overall, ARV-471 had been well tolerated; no deaths, DLTs, drug-related SAEs, or discontinuations due to toxicity had been reported. There were no hematologic toxicities reported. Three patients had completed at least 1 full cycle of 360 mg QD in Part A and no DLTs or other notable safety signals were reported, leading the CRC to recommend continued dose escalation.

As of 13 April 2021, no DLTs have been reported with ARV-471 monotherapy among the 45 patients treated in dose escalation and cohort expansion at doses up to 250 mg BID (500-mg total daily dose; N=6). In addition, 2 patients have received the 700-mg total daily dose for more than 28 days with no DLT. Therefore, the combination protocol will follow a simplified dose escalation with 2 escalation levels, 180 mg (rounded to 200 mg with availability of 100-mg tablets) and 400 mg. If there is no evidence of safety signal, the expansion can proceed with 200-mg and 500-mg QD doses in combination with palbociclib, based on the available safety data.

The starting dose of palbociclib is the approved dose and regimen, 125 mg once daily for 21 days followed by 7 days off treatment to complete a 28-day cycle. ARV-471 is a CYP3A4 substrate and palbociclib is a weak CYP3A inhibitor. Therefore, there may be an increased concentration of ARV-471 in the combination setting with palbociclib. Due to this potential, the starting dose of ARV-471 is 180 mg QD (rounded to 200 mg) to be given continuously (28-day cycle). PK sampling will be conducted to monitor for changes with the combination. These findings will be reviewed by the CRC in conjunction with Arvinas' CMO and recommendations for dose escalation will take these data into account. See details in [Section 2.4.5 Pharmacokinetic Drug Interactions](#).

Palbociclib is an FDA-approved agent with a well delineated side effect profile including hematologic toxicities (neutropenia, anemia, thrombocytopenia), pneumonitis and fatigue. Approximately 80% of patients develop neutropenia during treatment with palbociclib and, in combination with letrozole or fulvestrant, 66% of patients were reported to have absolute neutrophil counts ≤ 1000 (Grade 3 or higher). The hematologic toxicity is managed by dose modification and interruption. As of 06 Oct 2020, ARV-471 had no hematologic AEs reported and no identified risk factors for having marrow-related toxicity based on nonclinical data. Based on current knowledge, the current known toxicity profiles of ARV-471 and palbociclib are expected to be non-overlapping.

As of 01 November 2022, the safety profile of the combination of ARV-471 200 mg and palbociclib 125 mg was generally consistent with that observed after treatment with ARV-471 monotherapy (Study ARV-471-mBC-101 Part A dose escalation and Part B dose expansion), except for an increase in reported neutropenia (Data on File). The neutropenia was medically manageable, tolerable, and mostly asymptomatic in these patients. In the heavily pretreated patients from Part C, compared with historical data, there was an observed increase in palbociclib exposure in patients treated with ARV-471 in combination with palbociclib 125 mg. Cohort C5 is included to gain more understanding of the impact of ARV-471 on the clinical PK and safety of palbociclib 100 mg when given in combination with ARV-471.

To manage patients on this combination trial, the hematologic toxicities will be managed according to the palbociclib (IBRANCE®) USPI given the high likelihood of attribution to this agent. Non-hematologic AEs will be considered possibly attributable to the combination and/or either medication and will contribute to the definition of DLT for the combination regimen which is outlined in further detail in [Appendix 5](#).

4.3.4 Considerations for Dosing Schedule

Human PK predictions based on the PK studies performed in nonclinical species support a QD clinical dosing schedule.

Due to the limitation in the number of tablets that can be administered at one time with the current 10- and 50-mg tablet strengths, the option to evaluate a BID schedule was introduced to enable dosing at higher total daily doses. Assuming linear and time-independent PK, the total daily AUC of ARV-471 in a BID schedule is expected to be similar to the exposure achieved with a QD schedule for the same total daily dose. Consistent with this, BID dosing would be expected to result in a similar safety profile to that associated with the QD schedule at the same total daily dose. The BID dosing affords a viable option to assess exposure and thus, understand the PK, safety, and efficacy of ARV-471 at higher doses.

The initial BID dose may not exceed the concurrent QD experimental dose (not yet reviewed by CRC, but under evaluation) and may be rounded to a dose easily divided in 2. For example, the starting dose could be 180 mg BID or less if the total daily dose of 360 mg QD was being evaluated as a daily dose concomitantly. Alternatively, a lower dose may be selected dependent on the nature of the AEs or other factors (eg, PK). The starting dose for the BID dose-escalation cohort will be recommended by the CRC and will be based on the availability of safety and PK data.

4.4 Dose Modification Criteria

4.4.1 Dose Escalation

4.4.1.1 Part A – Phase 1 Dose Escalation

Dose escalation will be based on the CRC's review of all safety data from the patients enrolled into the cohort under review. In addition, PK data from the cohort under review may be considered, as appropriate. Details of data to be reviewed will be added to the CRC guidance document. AEs and SAEs will be tabulated by system organ class and preferred term. Laboratory test results after the first dose of ARV-471 will be summarized with regard to shift from baseline value and Common Terminology Criteria for Adverse Events (CTCAE) grade.

Dose escalation will be conducted according to a 3+3 design as described below and referenced in the Synopsis (see [Figure 2](#) and [Figure 3](#)).

If a DLT is observed in 1 of the 3 initial patients treated, 3 additional patients up to a total of 6 patients will be enrolled and treated at the same dose level. Patients not evaluable for DLT as outlined in [Appendix 5](#) (ie, not evaluable [NE] for assessment of MTD) will be replaced. If no further DLT is observed, the next dose level may be open after review and recommendation for

the next dose level by the CRC. Patients in Cycle 1 who for any reason other than toxicity did not receive at least 80% (22 of 28 doses of ARV-471) of their intended regimen will be replaced.

Dose escalation will continue until DLTs are observed in at least 2 of 6 patients treated at a dose level, leading to the conclusion that the MTD has been exceeded and ending dose escalation. Dose escalation may also stop when, upon further review, there is evidence of an exposure plateau, despite increasing dose. As of 13 April 2021, ARV-471 has had minimal AEs up to a dose of 500 mg and has not resulted in any DLTs (see the Investigator's Brochure for summary of available safety data). Further dose escalation may be warranted based on the rationale provided in the synopsis (refer to Dose Escalation in [Section 1.1](#)).

When a dose exceeding the MTD has been identified, the next lower dose is declared the MTD if 6 patients have already been treated at that dose. Otherwise, additional patients for a total of 6 patients will be treated at the next lower dose level, and if 0 or 1 patient have DLTs, this is declared the MTD. If 2 or more patients have DLTs, the dose will be de-escalated again according to the same scheme. The design continues until the MTD is declared.

An intermediate dose level between the one in which 2 DLTs occurred and the immediate lower level may be explored if deemed appropriate by the CRC.

If ≥ 2 patients in the intermediate dose level experience a DLT, no further dose escalation will occur; the MTD would be exceeded, and the previous lower dose level may be considered the MTD assuming 6 patients have been dosed at the previous lower dose level.

If > 6 patients have been treated in a cohort at or below the MTD, the CRC will re-evaluate the safety data at this dose level to confirm that this dose is the RP2D or may recommend a dose at an intermediate level.

At the discretion of the Principal Investigator, optional intra-patient dose escalation is permitted if the next higher dose level has been declared safe by the CRC and if the patient has had no Grade 2 or greater toxicities deemed related to study drug. Permission by the Medical Monitor is required.

[Figure 3](#) shows the Part A Dose Escalation Schema.

4.4.1.2 Part C Dose Escalation

The Part C dose-escalation levels for ARV-471 in combination with palbociclib will be 200 mg QD (Cohort C1; initially 180 mg QD but rounded up to 200 mg QD upon availability of the 100-mg tablets) and 400 mg QD (Cohort C2), and the expansion cohorts will be 500 mg QD (Cohort C3) and 200 mg QD (Cohort C4). The CRC will review all safety and PK data from the patients enrolled in the dose escalation cohorts and endorse dose escalation. Hematologic AEs will be considered related to palbociclib and will be managed according to the current palbociclib (IBRANCE®) USPI. DLTs (see [Appendix 5](#) for DLT definition) will be evaluated during the first (28-day) cycle. Patients in Cycle 1, who for any reason other than ARV-471 toxicity, do not receive at least 70% of each agent (eg, 15 doses of 21 planned for palbociclib irrespective of dose; or 20 of 28 doses of ARV-471) will be replaced.

Initially, up to 3 patients will be treated in Cohort C1 at 200 mg of ARV-471 (or 180 mg if prior to availability of the 100-mg tablets) in combination with the recommended dose of palbociclib as per the USPI (125 mg QD). If a DLT, as defined specifically for Part C (see [Appendix 5](#)), is observed in 1 of the 3 initial patients treated, 3 additional patients will be enrolled and treated at the same dose level. Alternatively, if there are related Grade 2 or 3 non-hematologic AEs of clinical significance as determined by the CRC, 3 additional patients may also be treated at the same dose level. If there are no DLTs, or if there is 1 DLT out of 6 patients, then the CRC will review and approve escalation to Cohort C2, at the 400-mg QD dose with palbociclib. The same review process will be followed for escalation to Cohort C3, in which approximately 20 patients will receive ARV-471 at 500 mg QD with palbociclib. In expansion Cohort C4, approximately 20 patients will receive ARV-471 at 200 mg QD with palbociclib.

An intermediate dose level below 500 mg QD may be recommended by the CRC for expansion Cohort C3. If a second DLT is observed in any given dose-escalation cohort, the dose level will be considered to have exceeded the MTD, dose escalation will stop, and the dose will be reduced to the next lower dose level deemed safe by the CRC or an intermediate dose level may be tested. The dose of ARV-471 that is administered in combination with palbociclib will not exceed the highest dose cleared in Part A. Approximately 40 patients (approximately 20 each in Cohorts C3 and C4) are expected to receive ARV-471 in combination with palbociclib after the dose-escalation phase of the combination cohort and those patients will be monitored by the SRC.

4.4.2 Dose Interruption and Modification

The ARV-471 dose levels are shown in [Table 14](#), along with necessary rounding upon availability of the 100-mg tablet strength, as well as the recommended dose levels to be utilized for dose reduction due to toxicity. The dose-level reductions shown in this table should be implemented in accordance with the guidance in the following sections. In the event that the ARV-471 dose is escalated beyond 700 mg total daily dose, similar guidelines for rounding (to allow for the 100-mg tablet) and dose reduction (in 100-mg increments) will apply.

Table 14 ARV-471 Dose Levels and Recommended Modifications

ARV-471 starting dose (total daily dose)	Rounded dose ^a	1 st dose-level reduction ^b	2 nd dose-level reduction ^b
700 mg ^c	NA	500 mg	400 mg
500 mg ^c	NA	400 mg	300 mg
400 mg	NA	300 mg	200 mg
360 mg	400 mg	300 mg	200 mg
200 mg	NA	100-150 mg ^d	50-100 mg ^d
180 mg	200 mg	100-150 mg ^d	50-100 mg ^d

- Upon availability of the 100-mg tablet, the total daily dose for each patient is rounded to account for this available tablet strength.
- Alternate dose reductions may be considered depending on the clinical context.
- As PK analyses suggest similar exposure resulting from the QD and BID dosing (see [Section 4.3.4](#)), patients on a BID schedule may transition to receive the same total daily dose on a QD schedule, upon availability of the 100-mg tablets.
- The Medical Monitor should be consulted for determination of the appropriate dose reduction.

4.4.2.1 Parts A and B Dose Interruption and Modification

Dose interruption and/or reduction by the Principal Investigator and in consultation with the Medical Monitor will be performed as follows for both Part A and Part B of this study ([Table 15](#)). Additional information for dose reduction in Part A can be found in [Figure 3](#). All related Grade 3 AEs should have their dose interrupted until return to $\leq$ Grade 1 or baseline. Study drug may be resumed using the modification guidelines below:

Table 15 Dose Interruption and/or Reduction for Parts A and B

Related Grade 3^a AEs	ARV-471 Dose Modification^b
First Dose Reduction	Reduce by 1 dose level ^{c, d}
Second Dose Reduction	Reduce previous dose by 1 dose level ^{c, d}
Third Dose Reduction	Discontinue ARV-471 ^e
Grade 4 AE	Discontinue ARV-471 ^f

Abbreviations: AE=adverse event.

a. Grade 3 AEs not requiring dose reduction:

- I. Grade 3 fatigue lasting <7 days;
- II. Grade 3 lymphopenia lasting <72 hours.
- III. Grade 3 nausea/vomiting/diarrhea lasting <72 hours in the absence of maximal medical therapy

b. See [Table 14](#).

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

d. If the patient has demonstrated significant benefit, the AE was rapidly reversible, and redosing is not expected to pose a significant risk to the patient, dose re-escalation of ARV-471 may be considered after consultation with the Medical Monitor

e. If the patient appears to be clinically benefiting despite prior dose reduction and is not considered at significant risk for serious AEs, a further dose reduction may be considered in consultation with the Medical Monitor

f. If the patient has demonstrated significant benefit, the AE was rapidly reversible, and redosing is not expected to pose a significant risk to the patient, resumption of ARV-471 at a reduced dose may be considered dependent on the nature of the Grade 4 AE after consultation with the Medical Monitor

Definitions for DLT, MTD, and RP2D are presented in [Appendix 5](#). The criteria for stopping study drug treatment in individual patients are presented in [Section 4.5.1](#). The criteria for stopping dose escalation are presented in [Section 4.5.2](#).

4.4.2.2 Part C Dose Interruption and Modification

Dose interruption and/or reduction by the Principal Investigator after consultation with the Medical Monitor will be performed as follows:

Non-hematologic AEs: Dose interruption and modification will proceed as follows taking into account guidance on both agents:

For related Grade 3 non-hematologic toxicity, both ARV-471 and palbociclib will be held until symptoms resolve to Grade 1 or Baseline. Then ARV-471 will resume with a dose reduction as per [Table 14](#) and palbociclib will resume at the next lower dose level according to specific guidance for non-hematologic toxicity in the palbociclib USPI and provided in [Table 17](#) for convenience. For related Grade 4 AEs, Investigators should follow the guidance in [Table 16](#). If ARV-471 is permanently discontinued, palbociclib will also be discontinued on study.

Table 16 Dose Interruption and/or Reduction for Part C

Non-hematologic toxicity	ARV-471	Palbociclib
Related Grade 3 AE	Hold until symptoms are $\leq$ Grade 1; restart at a reduced dose as per Table 14 .	Hold until symptoms are $\leq$ Grade 1 then resume at next lower dose
Related Grade 4 AE	Discontinue ARV-471 ^a	Hold until symptoms are $\leq$ Grade 1 then resume at next lower dose (if ARV-471 is discontinued, then palbociclib will also be discontinued)

a. If the patient has demonstrated significant benefit, the AE was rapidly reversible, and redosing is not expected to pose a significant risk to the patient, resumption of ARV-471 at a reduced dose may be considered dependent on the nature of the Grade 4 AE after consultation with the Medical Monitor.

Table 17 Palbociclib Dose Modification and Management – Non-hematologic Toxicities

CTCAE Grade	Dose Modification
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-hematologic toxicity (if persisting despite optimal medical treatment)	Withhold until symptoms resolve to: - Grade ≤ 1 - Resume at the next lower dose.
Grading according to CTCAE 5.0. CTCAE: Common Terminology Criteria for Adverse Events	

Hematologic toxicity: Related hematologic AEs will be considered related to palbociclib and follow dose modification guidance of the palbociclib USPI, provided below for convenience.

If Grade ≥ 3 hematologic toxicity occurs, palbociclib dosing will be interrupted; see [Table 19](#) below. ARV-471 dosing will continue unless hematologic toxicity symptoms persist without improvement 1 week after dose interruption of palbociclib at which time ARV-471 (and palbociclib) will be held until symptoms improve to Grade ≤ 2 . Once the patient meets criteria to restart, ARV-471 may be restarted at the same dose and palbociclib may be re-initiated as per dose modification [Table 18](#) (per USPI).

Patients who have their palbociclib dose modified will be permitted to continue to receive ARV-471. Patients unable to resume palbociclib or to receive at least 70% of the scheduled doses of palbociclib for the first cycle (15 of 21 planned doses), will be replaced. Patients who are replaced but who may continue to benefit from ARV-471 may continue, at the Investigator's discretion, to receive ARV-471 at their current dose. However, patients who have ARV-471 discontinued will not be allowed to continue to receive palbociclib on study.

Table 18 Palbociclib Recommended Dose Modifications for Adverse Events

Dose Level	Dose for Cohorts C1-C4	Dose for Cohort C5
Recommended starting dose	125 mg/day	100 mg/day
First dose reduction	100 mg/day	75 mg/day*
Second dose reduction	75 mg/day*	n/a

* If further dose reduction below 75 mg/day is required, discontinue.

Table 19 Palbociclib Dose Modification and Management – Hematologic Toxicities ^a

Monitor complete blood counts prior to the start of palbociclib therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.	
CTCAE Grade	Dose Modification
Grade 1 or 2	No dose adjustment is required.
Grade 3	<u>Day 1 of cycle:</u> Withhold palbociclib, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤ 2, start the next cycle at the same dose. <u>Day 15 of first 2 cycles:</u> If Grade 3 on Day 15, continue palbociclib at current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reductions in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 neutropenia ^b with fever $\geq 38.5^{\circ}\text{C}$ and/or infection	<u>At any time:</u> Withhold palbociclib until recovery to Grade ≤ 2. Resume at the next lower dose.
Grade 4	<u>At any time:</u> Withhold palbociclib until recovery to Grade ≤ 2. Resume at the next lower dose.

Grading according to CTCAE 5.0

CTCAE: Common Terminology Criteria for Adverse Events; LLN: lower limit of normal

- Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, eg, opportunistic infections).
- Absolute neutrophil count (ANC): Grade 1: ANC < LLN to 1500/mm³; Grade 2: ANC 1000 to <1500/mm³; Grade 3: ANC 500 to < 1000/mm³; Grade 4: ANC <500/mm³

4.5 Stopping Criteria

The stopping criteria for individual patients (Section 4.5.1) and the study (Section 4.5.3) are the same for Part A – Phase 1 Dose Escalation, Part B – Phase 2 Cohort Expansion, and Part C – Combination. The stopping criteria to end dose escalation for Part A and Part C are outlined in Section 4.5.2.

4.5.1 Criteria for Stopping Individual Patients

Dosing for any individual patient may be stopped if the patient experiences a possibly or probably drug-related DLT or a clinically significant possibly/probably drug-related AE, which in the opinion of the Principal Investigator, or Sponsor's medical representative, warrants discontinuation of the study for that patient's well-being.

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

Part A and B: Permanent discontinuation criteria:

ARV-471 treatment should be permanently discontinued for the following:

- Any sustained Grade 3 non-skin drug-related AE lasting >7 days
- Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
- Any of the following drug-related liver function test abnormalities that meets the following criteria require discontinuation:
 - AST or ALT >8× upper limit of normal (ULN) ○ AST or ALT >5× ULN for >2 weeks
 - AST or ALT >3× ULN and either total bilirubin >2× ULN or International normalized ratio (INR) >1.5
 - ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Any dosing interruption lasting >28 days from the next scheduled dose with the following exceptions:
 - Dosing interruptions >28 days that occur for non-drug-related reasons may be allowed if approved by the Sponsor. Prior to re-initiating treatment in a patient with a dosing interruption lasting >28 days, the Sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued ARV-471 treatment.

Part C: Permanent discontinuation criteria:

Discontinue ARV-471 and palbociclib for the same criteria listed in Part A and B above, except:

- Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding

4.5.2 Criteria for Stopping Dose Escalation in Part A and C

If DLTs are observed in at least 2 of 6 patients treated at a dose level, it will be concluded that the MTD has been exceeded and dose escalation will end. Dose escalation may also stop if other factors suggest dose escalation should be halted (eg, long term tolerability, pharmacodynamic findings, plateauing of absorption).

4.5.3 Criteria for Stopping the Study

The Sponsor may terminate this study prematurely, either one Part (A, B or C), 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.

4.5.4 End of Study Definition

A patient is considered to have completed the study if they have completed all phases of the study, including the last visit or the last scheduled procedure as shown in the Schedule of Activities (SoA; [Section 1.3](#)).

The end of the study is defined as the date of the last visit of the last patient in the study or the last scheduled procedure as shown in the SoA ([Section 1.3](#)) for the last patient in the study.

For patients on study after implementation of Protocol Amendment 6, see [Table 8](#), [Table 9](#), [Table 10](#), and [Section 4.5.5](#).

4.5.5 Rationale for Patients Continuing on Treatment After Primary Study Completion

Throughout Protocol Amendment 6, guidance is provided for patients who continue to receive study treatment after the primary study completion date. This date will be at least 6 months after the LPFV, which allows for evaluation of the key study objectives. Patients are permitted to continue to receive study treatment once the primary completion date is achieved if, in the opinion of the Investigator, they are continuing to receive benefit from the study treatment. Investigators will continue to refer to the protocol and follow the SoA as described in [Table 8](#), [Table 9](#), and [Table 10](#).

Protocol Amendment 6 provides instructions for a modified visit schedule with reduced eCRF data collection that will begin after implementation of the amendment. Changes described in Protocol Amendment 6 can be implemented at clinical sites once IRB approval of this amendment is obtained. For patients who continue to receive treatment after implementation of

Protocol Amendment 6, Investigators will continue to report AEs leading to discontinuation of study treatment and SAEs as detailed in [Appendix 4](#). Clinical data generated from new patient visits will continue to be collected in site source and select data will be entered into the eCRF. Additionally, as noted in [Table 8](#), [Table 9](#), and [Table 10](#), patients continuing to experience treatment-related toxicity at the time of EOT will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. The Investigator will continue to follow the protocol, and notify the Medical Monitor, when necessary, as per the protocol (eg, intolerable AEs, dose modification).

5. STUDY POPULATION

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

5.1 Inclusion Criteria

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

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C – Phase 1b Combination
1	Patients at least 18 years of age at the time of signing the informed consent.	Same	Same
2	Patients must have histologically or cytologically confirmed ER+ and HER2- advanced breast cancer. Advanced breast cancer is metastatic, recurrent, or locally advanced unresectable breast cancer for which standard curative therapy is no longer effective or does not exist. a. ER+ disease must be documented by IHC per ASCO/CAP Guidelines (Hammond et al., 2010). b. HER2- disease must be documented by either IHC or in-situ hybridization per ASCO/CAP guidelines (Wolff et al., 2018).	Same	Same
3	Patients must have measurable or nonmeasurable disease by RECIST 1.1, with radiologic tumor assessments performed within 28 days of the first dose of therapy.	Same	Same
4	Women must be postmenopausal due to surgical or natural menopause, which requires at least 1 of the following: (a) prior bilateral oophorectomy, (b) age ≥ 60 years, (c) age < 60 years and amenorrhoeic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol levels in the postmenopausal range; or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin. Patients on ovarian suppression therapy should remain on such therapy in the absence of intolerable symptoms.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C – Phase 1b Combination
5	Men must agree to use contraception as detailed in Appendix 6 of this protocol during the treatment period and for 6 months after the last dose of study treatment and refrain from donating sperm during this period.	Same	Same
6	Patients must have received: - at least 2 prior endocrine regimens in any setting (neoadjuvant, adjuvant or advanced/metastatic) - a CDK4/6 inhibitor - up to 3 prior regimens of cytotoxic chemotherapy in the locally advanced or metastatic setting All such therapy must be discontinued at least 14 days prior to enrollment.	Patients must have received: - at least 1 prior endocrine regimen for a minimum of 6 months in the locally advanced or metastatic setting; if more than 1 prior endocrine regimen has been administered, only 1 of the regimens must have been administered for a minimum of 6 months in the locally advanced or metastatic setting - a CDK4/6 inhibitor - up to 1 prior regimen of cytotoxic chemotherapy in the locally advanced or metastatic setting The patient must have had evidence of disease progression while receiving their last endocrine-based therapy. All such therapy must be discontinued at least 14 days prior to enrollment.	Patients must have received: - At least 1 prior endocrine regimen - No more than 2 prior chemotherapy regimens for advanced disease. All such therapy must be discontinued at least 14 days prior to enrollment.

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C – Phase 1b Combination
7	Patients must be willing to undergo a core biopsy of accessible tumor within 4 weeks prior to the initiation of study treatment and a follow-up biopsy on-treatment for ER IHC testing and PD studies. (Patients without accessible tumor tissue may be eligible after discussion with the Medical Monitor).	Same	Same
8	Patients must have 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): a. ANC of $\geq 1500/\text{mm}^3$ or $\geq 1.5 \times 10^9/\text{L}$. b. Platelets of $\geq 100,000/\text{mm}^3$ or $\geq 100 \times 10^9/\text{L}$. c. Hemoglobin ≥ 9 g/dL.	Same	Same
9	aPTT $\leq 1.25 \times \text{ULN}$ and INR ≤ 1.25 .	aPTT $\leq 1.25 \times \text{ULN}$ and INR ≤ 1.25 unless the patient is receiving anticoagulation, then aPTT and INR should be within the therapeutic range of the intended use.	aPTT $\leq 1.25 \times \text{ULN}$ and INR ≤ 1.25 unless the patient is receiving anticoagulation, then aPTT and INR should be within the therapeutic range of the intended use.
10	Patients must have adequate renal function defined as serum creatinine of $\leq 1.5 \times \text{ULN}$ or an estimated creatinine clearance of ≥ 50 mL/min by Cockcroft Gault.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C – Phase 1b Combination
11	Patients must have adequate liver function defined as: a. Total serum bilirubin of $\leq 1.5 \times$ ULN unless the patient has documented Gilbert syndrome. b. AST and ALT of $\leq 2.5 \times$ ULN if there is <u>NO</u> liver involvement secondary to tumor OR $\leq 5.0 \times$ ULN if there is liver involvement secondary to tumor.	Same	Same
12	Any toxicity from prior anti-cancer therapy other than alopecia must have resolved to baseline severity or Grade ≤ 1 NCI CTCAE version 5.0	Same	Same
13	Patients must agree and be capable of taking oral medication without crushing, dissolving, or chewing tablets/capsules.	Same	Same
14	Patients must have an ECOG Performance Status of 0 or 1	Same	Same
15	Patients must be willing and capable of giving signed informed consent and comply with the requirements and restrictions listed in the ICF and in the protocol.	Same	Same

Abbreviations: aPTT=activated partial thromboplastin time; ANC=absolute neutrophil count; ALT=alanine aminotransferase; ASCO=American Society of Clinical Oncology; AST=aspartate aminotransferase; CAP=College of American Pathologists; CDK=cyclin-dependent kinase; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; FSH=follicle-stimulating hormone; HER2=human epidermal growth factor 2; ICF=informed consent form; IHC=immunohistochemistry; INR=international normalized ratio; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PD=pharmacodynamic; RECIST 1.1=Response Evaluation Criteria In Solid Tumors version 1.1; ULN=upper limit of normal.

5.2 Exclusion Criteria

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

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
1	Patients with known symptomatic brain metastases requiring steroids (above physiologic replacement doses). Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to first dose of study drug, have discontinued high dose corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable as judged by the Investigator.	Same	Same
2	Patients who have received 4 or more regimens of chemotherapy for locally advanced or mBC.	Patients who have received more than 1 regimen of chemotherapy for locally advanced or mBC	Patients who have received more than >2 regimens of chemotherapy for advanced/metastatic disease (regardless of prior adjuvant chemotherapy use) in addition to endocrine therapy.
3	Patients who have received prior anticancer or other investigational therapy within 14 days prior to the first administration of study drug. For prior therapies with a half-life longer than 3 days, the interval must equal 28 days prior to the first administration of study drug and the patient must have documented disease progression.	Same	Same
4	Patients who have initiated therapy with bone-modifying agents (bisphosphonates, denosumab, or similar) within 14 days of enrollment. (Patients who are receiving bone-modifying agents are eligible for this study provided the bone-modifying agent was started more than 14 days prior to study enrollment.)	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
5	Patients with active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus, hepatitis C virus, known HIV, or AIDS-related illness. In equivocal cases, patients whose viral load is negative may be eligible. HIV-seropositive patients who are healthy and low risk for AIDS-related outcomes could be considered eligible. Eligibility criteria for HIV-positive patients should be evaluated and discussed with the Medical Monitor and will be based on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions (eg, opportunistic infections), and status of HIV treatment.	Same	Same
6	Major surgery (as defined by the Investigator) within 4 weeks of first dose of study drug.	Same	Same
7	Radiation therapy within 4 weeks of first dose of study drug or prior irradiation to >25% of the bone marrow. Palliative radiation for the alleviation of pain due to bone metastasis will be allowed during the study.	Same	Same
8	Previous high-dose chemotherapy requiring stem cell rescue.	Same	Same
9	Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen in this study. Patients with a prior or concurrent malignancy whose natural history or treatment that does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen in this study may be eligible but must be discussed with the Medical Monitor.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
10	Prior treatment with ARV-471.	Same	Same
11	Any of the following in the previous 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease.	Same	Same
12	Any of the following in the previous 6 months: congenital long QT syndrome, Torsade de Pointes, arrhythmias (including 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). If a patient has a cardiac rhythm device/pacemaker placed and QTcF ≤ 470 msec, the patient can be considered eligible. Patients with cardiac rhythm device/pacemaker must be discussed in detail with the Medical Monitor to judge eligibility.	Same	Same
13	History of symptomatic cardiac valve disease. Patients with mitral valve prolapse which is asymptomatic or not associated with clinically significant sequelae (eg, mitral regurgitation) are eligible. Any case of mitral valve prolapse must be discussed with the Medical Monitor prior to enrollment to confirm eligibility.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
14	Other acute or chronic severe medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.	Same	Same
15	Active inflammatory gastrointestinal disease, chronic diarrhea, or previous gastric resection or lap band surgery. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed unless it meets a criterion under Exclusion Criterion #17.	Same	Same
16	Patients who fall into any of the following: a. Investigational site staff members directly involved in the conduct of the study and their family members; OR b. Site staff members otherwise supervised by the Investigator; OR c. Patients employed by the Sponsor who are directly involved in the conduct of the study.	Same	Same
17	Concurrent administration of medications or foods that are strong inhibitors and inducers of cytochrome P450 3A4, sensitive substrates of CYP2B6 or those with narrow therapeutic indices, sensitive P-gp substrates or those with narrow therapeutic indices, and any medications that are known to prolong the QT interval (see Appendix 9). Prior use must be discontinued 2 weeks (1 week for medications that are known to prolong the QT interval) before the start of study drug treatment.	Same	Same

No.	Part A – Phase 1 Dose Escalation	Part B – Phase 2 Cohort Expansion	Part C-Phase 1b Combination
18	n/a	n/a	Discontinuation or dose reduction of prior palbociclib due to: • Interstitial lung disease • Grade 3 or 4 toxicity (patients previously dose reduced for toxicity may be considered eligible with approval by Medical Monitor) • Hypersensitivity
19	QTcF > 470 msec.	Same	Same

Abbreviations: AIDS=acquired immunodeficiency syndrome; AR=androgen receptor; AST=aspartate aminotransferase; CD=cluster of differentiation; GI=gastrointestinal; HIV=human immunodeficiency virus; mBC=metastatic breast cancer; n/a=not applicable; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; P-gp=P-glycoprotein; QTcF=corrected QT interval by Fridericia's method.

5.3 Lifestyle Considerations

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

- For QD schedule total ARV-471 dose is to be taken within a 2-hour period and at approximately the same time each day.
- Patients should apply sunscreen products and avoid excessive sun exposure during study drug treatment.

Grapefruit, including grapefruit juice, may interact with palbociclib. Patients enrolled in Part C should not consume grapefruit containing products while on treatment with palbociclib.

5.4 Screen Failures

Screen failures are defined as patients who consented to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. Rescreened patients should not be assigned the same patient number as the one they received in the initial screening.

6. STUDY TREATMENT

ARV-471 will be administered orally with food (eg, a light meal of approximately 400 to 600 calories which includes a mixture of fat, carbohydrates, and protein), in continuous dosing over 28-day cycles. The ARV-471 dose and schedule are specific for each study part/cohort, as described under Study Design ([Section 4](#)) and Dose Escalation ([Section 4.4.1](#)). Upon availability of the 100-mg tablet, the total daily dose for each patient is adjusted/rounded to account for the available tablet strength (ie, patients receiving 180 mg QD begin receiving a rounded dose of 200 mg QD, while patients receiving 360 mg QD begin receiving a rounded dose of 400 mg QD).

Patients in Part C will also receive palbociclib according to the recommended starting dose and regimen (125 mg once daily for 21 days followed by 7 days off treatment) as per the approved palbociclib (IBRANCE®) USPI. In Cohorts C1-C4, palbociclib will be administered at the same time as ARV-471. During the dose escalation portion of Part C, patients must start at the standard full dose of palbociclib. Once a recommended dose of ARV 471 in combination with palbociclib has been determined, patients previously treated with palbociclib at a reduced dose may be allowed to enroll at a lower palbociclib dose in consultation with the Arvinas Medical Monitor (see Exclusion Criterion #18).

In Cohort C5, in Cycle 1, palbociclib 100 mg will be given alone for 8 days (C1D1 through C1D8), prior to starting ARV-471 200 mg QD on Cycle 1 Day 9. Palbociclib 100 mg QD will begin on C1D1 and be given for 21 days followed by 7 days off treatment ([Figure 1](#)). In Cycles 2 and beyond, patients will receive, starting on Day 1, ARV-471 200 mg QD continuously and palbociclib 100 mg QD for 21 days followed by 7 days off-treatment.

A patient may continue treatment at the discretion of the Principal Investigator until a treatment discontinuation criterion is met (see [Section 7.1](#)). Patients who have evidence of radiographic disease progression may be considered for continued study therapy provided the Principal Investigator has determined that they are still benefiting from study therapy. All such requests must be reviewed and approved by the Sponsor's Medical Monitor.

6.1 Study Treatment Administered

For the purposes of this study, “study treatment” is defined as any investigational treatment intended to be administered to a patient according to the study protocol.

See [Table 20](#) for more information about ARV-471 and palbociclib. See the Pharmacy Manual for the full description of study treatments.

Table 20 Study Treatment Details

Study Treatment Name	ARV-471
Dosage Formulation	Tablets
Route of Administration	Oral
Dosing Instructions	Patients will take ARV-471 by mouth QD or BID with food (eg, a light meal of approximately 400 to 600 calories which includes a mixture of fat, carbohydrates, and protein) in continuous daily dosing (on 28-day cycles).
Packaging and Labeling	Study treatment will be provided in a high-density polyethylene bottle with child-resistant cap. Each bottle will be labeled as required per US regulations.

Study Treatment Name	Palbociclib (IBRANCE®)
Dosage Formulation	Capsules
Route of Administration	Oral
Dosing Instructions	Patient will take Palbociclib (IBRANCE®) once daily with food for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.
Packaging and Labeling	Study treatment is an FDA-approved marketed product and will be provided in the approved commercial high-density polyethylene bottle with child-resistant cap. Each bottle will have a clinical over-label to identify it as clinical trial material.

6.2 Measures to Minimize Bias

This is an open label Phase 1/2 study. If multiple cohorts are open to accrual simultaneously, sequential patients may be enrolled to each cohort in an alternating fashion.

6.3 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in [Section 4.4.2](#). Any departures from the intended regimen must be recorded in the eCRFs.

ARV-471 will be administered orally, QD or BID 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. Patients will self-dose as described above, with the exception of doses that will be administered at the clinic. Patients enrolled in Part C Cohorts C1-C4 will initially receive palbociclib, 125 mg QD, to be taken on days 1-21 of each cycle with ARV-471. Patients enrolled in Part C Cohort C5, will initially be treated with palbociclib 100 mg QD starting on C1D1, for 21 days followed by 7 days off and ARV-471 200 mg QD will start on Cycle 1 Day 9 and be given continuously.

On scheduled clinic visits, palbociclib should be withheld and taken while in the clinic.

At each clinic visit, prior to dispensing additional study treatment, the previously dispensed ARV-471 study treatment (and palbociclib) in its respective bottle will be retrieved by the study center personnel and compliance assessed. Patients will be required to return all bottles and remaining tablets of ARV-471 (and bottles and remaining capsules of palbociclib for Part C), as well as the completed patient diary for drug accountability and documentation of food consumption. Patients are to complete patient diary daily during study participation. Patients exhibiting poor compliance as assessed by tablet or capsule counts should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking less than 80% or more than 120% of assigned study drug during any evaluation period (visit to visit) for Part A and less than 70% or more than 120% for Part C.

6.3.1 Treatment Compliance for Patients on Study After Implementation of Protocol Amendment 6

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in [Section 4.4.2](#). Any differences from the intended regimen must be recorded in the appropriate site source documentation system.

Treatment compliance remains as described in [Section 6.3](#) and will be monitored by drug accountability and documented in site source documents. Dosing diaries no longer need to be completed by the patient.

6.3.2 Treatment Strategy

The clinical staff is responsible for the ongoing safety and well-being of the patients while they are in the study center. Equipment and emergency drugs should be available to treat common medical emergencies that might occur.

6.3.3 Warnings and Precautions

As this is the first administration of ARV-471 to humans, all effects cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. AEs with palbociclib and ARV-471 are anticipated to be non-overlapping based on early clinical and preclinical data. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

Please refer to the palbociclib (IBRANCE®) USPI for warnings and precautions related to palbociclib.

6.4 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and physiologic replacement doses of systemically administered corticosteroids) that the patient is receiving at the time of enrollment (within 28 days before the time of enrollment) or receives during the study until the follow-up visit or 30 days after the last dose of study medication will 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.

Palliative radiotherapy on study is permitted (eg, skeletal administration for mBC), but should be discussed with the medical monitor prior to initiation. Bisphosphonates and RANKL inhibitors are allowed. Paracetamol/acetaminophen at doses of ≤ 2 g/day is permitted for use any time during the study. Herbal supplements 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.

6.5 Excluded Medications/Therapy

Other therapies with known anti-cancer effects are prohibited during study participation. Ovarian suppression therapy with gonadotropin-releasing hormone (GnRH) agonists is not considered anti-cancer therapy and is allowed.

Patients enrolled in this clinical study will not be allowed to receive the medications listed below (see [Appendix 9](#) for details). Unless otherwise specified, these medications should be discontinued at least 14 days prior to starting ARV-471. Of note, if a patient signed consent under a prior protocol version, they may continue following the Excluded Medications/Therapy

section of that protocol version at the discretion of the Investigator and after discussion with the Medical Monitor:

- strong inducers/inhibitors of CYP3A4
- sensitive substrates of CYP2B6 or those with narrow therapeutic indices
- 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
- excluded medications in the palbociclib USPI for Part C.
- moderate CYP3A4 inhibitors/inducers during Cycle 1 in Part C Cohort C5

6.6 Patient Dose Modification Review

The details of dose selection, dose escalation, dose reduction, and study stopping criteria are described in the Study Design ([Section 4](#)) of this protocol.

6.7 Treatment After the End of the Study

The Sponsor will not provide any additional care to patients after they leave the study. Patients should continue their care as normally expected for patients with locally advanced or mBC.

7. DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

The process for dose escalation and the stopping criteria for the study are described in the Study Design ([Section 4](#)).

Patients will be treated until disease progression (radiographic and/or clinical progression), unacceptable toxicity, or withdrawal of consent but may be discontinued from study treatment at any time. Specific reasons for treatment discontinuation include but are not limited to the following:

- Radiographic and/or clinical disease progression
- Severe noncompliance with the protocol
- Consent withdrawal
- Pregnancy
- Death

Discontinuation of study treatment for abnormal liver function: see [Section 4.5.1](#).

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 at an individual study site may include but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to any patient enrolled in the study.
- The Sponsor's decision to suspend or discontinue further testing or evaluation of the drug under study.
- CRC/SRC recommendation.
- 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 Patient Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before the withdrawal of consent.

If a patient withdraws from the study, they may request destruction of any tissue/cell/plasma samples taken and not tested, and the Investigator must document this in the study center study records.

See the SoA ([Section 1.3](#)) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Should a patient request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Patients withdrawing due to an AE should be followed-up according to the follow-up visit.

Patients who voluntarily withdraw are termed dropouts. If a patient has received less than 80% of the assigned dosing regimen in the first cohort for Part A or less than 70% of the assigned regimen for Part C for reasons other than toxicity, he/she will not be deemed DLT evaluation eligible and will be replaced.

Patients withdrawn due to an AE will not be replaced.

7.3 Lost to Follow-up

Patients will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study center.

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

- The study center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he will be considered to have withdrawn from the study.

Discontinuation of specific study centers or of the study as a whole is described in [Appendix 2](#).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in [Section 1.3](#).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor (or designee) immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

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 patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

The maximum amount of blood volumes collected from each patient over the duration of a cycle will not exceed 500 mL, including any extra assessments that may be required. Additional information on blood volumes is detailed in the Laboratory Manual. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Please refer to [Appendix 10](#) for guidelines related to the ongoing COVID-19 pandemic, including vaccine administration, the use of video TeleMed visits, shipment of drug supply, and treatment of patients testing positive for COVID-19.

8.1 Safety Assessments

In this study, safety will be evaluated through AE monitoring, clinical evaluations (ie, vital signs, PE, electrocardiograms [ECGs]), and laboratory tests (ie, hematology, serum chemistries).

Any clinically significant changes, in the opinion of the Investigator, noted during abbreviated or full PE, ECG evaluations, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the appropriate AE page of the eCRF so that the Sponsor or designee can collect additional information about that abnormality, including information regarding relationship to study drug or other causes, any action taken, and outcome.

Planned time points for all safety assessments are provided in the SoA ([Section 1.3](#)).

8.1.1 Physical Examinations

A full PE is required at Screening and abbreviated PEs should be performed as appropriate at each visit where complete PEs are not required. PE may be performed within 48 hours prior to a scheduled visit. There is no need to repeat PE if baseline assessment is within 96 hours on C1D1.

A complete PE will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Musculoskeletal, and Neurological systems. An abbreviated PE will be symptom directed. Height and weight will also be measured and recorded as part of routine PE.

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

8.1.2 Vital Signs

Oral or tympanic temperature, pulse rate, blood pressure, and respiratory rate will be assessed. Blood pressure and pulse measurements will be assessed while the patient 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.

Blood pressure and pulse measurements should be preceded by approximately 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

On Day 1 of each cycle, vital signs should be measured prior to dosing (pre-dose). Blood pressure and pulse rate will be repeated 1 hour after study drug dosing. See the SoA (see [Section 1.3](#)) for more information.

8.1.3 Electrocardiograms

The screening ECG will be a single 12-lead ECG. At all other times, at each time point, triplicate 12-lead ECGs will be performed to determine mean QT interval corrected using Fridericia's method (QTcF) interval. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

Triplicate or single 12-lead ECG will be obtained as outlined in the SoA (see [Section 1.3](#)) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs should be confirmed by qualified personnel at the institution.

When coinciding with blood sample draws for PK, ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>60 msec increase from baseline or >500 msec), the ECGs should be re-evaluated by qualified personnel at the institution for confirmation.

Additional triplicate ECGs may be performed as clinically indicated. Refer to [Section 7.1](#) for discontinuation criteria.

If a clinically significant ECG finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the Investigator or qualified designee will determine if the patient can continue in the study and if any change in patient management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding will be reported as an AE. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the patient to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the patient to continue in the study.

8.1.4 Echocardiogram

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

8.1.5 Clinical Safety Laboratory Assessments

See [Appendix 3](#) for the list of clinical laboratory tests to be performed and to the SoA ([Section 1.3](#)) for the timing and frequency.

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 eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease/patient's health status, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 35 days after the last dose of study treatment 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 judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in [Appendix 3](#), must be conducted in accordance with the Laboratory Manual and the SoA ([Section 1.3](#)).

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

8.1.6 Pregnancy

A serum pregnancy test will be conducted on all women of childbearing potential at Screening. Urine pregnancy tests will be done on study.

A woman is considered postmenopausal (not of childbearing potential) if at least 1 of the following criteria are met: (a) prior bilateral oophorectomy, (b) age ≥ 60 years, (c) age < 60 years and amenorrhoeic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol levels in the postmenopausal range; or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a GnRH agonist such as goserelin.

The Investigator or qualified designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart ([Appendix 6](#)).

In addition, the Investigator or qualified designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

Male patients who are able to father children will need to affirm that they meet the criteria for the correct use of 2 of the selected methods of contraception ([Appendix 6](#)).

8.2 Efficacy Assessments

To meet the study's secondary objectives related to assessment of anti-tumor response, preliminary anti-tumor activity of ARV-471 and the combination of ARV-471/palbociclib will be evaluated through assessment of imaging, available tumor markers and other biomarkers.

Planned time points for all efficacy assessments are provided in the SoA ([Section 1.3](#)).

8.2.1 Radiographic Imaging

Radiographic imaging, computed tomography (CT) or magnetic resonance imaging (MRI) for all known or suspected disease sites, is required during Screening and during study drug treatment using the same imaging techniques. Scan intervals should be scheduled based on C1D1, not the previous scan. In particular, the Week 24 scan should be scheduled in advance to ensure it is performed in the specified protocol timelines as shown in the SoA ([Section 1.3](#)). Timepoints are fixed based on the calendar, regardless of treatment delays. Tumor assessments are to continue until discontinuation of study treatment, initiation of subsequent systemic anti-cancer therapy, or withdrawal of consent, whichever occurs first.

Bone scans must be performed in all patients at baseline within 28 days prior to C1D1. If bone scans are not available or cannot be scheduled readily, CT/MRI scan with bone windows can be sufficient. Bone scans performed > 28 to 45 days prior to enrollment as part of clinical care

unrelated to this study may be acceptable pending discussion with the Medical Monitor. For patients with bone lesions identified only by bone scan at baseline, additional studies (eg, X-ray, CT scan with bone windows or MRI) must be performed of these lesions for follow-up assessment.

Imaging techniques are to follow RECIST 1.1 guidelines as summarized in [Appendix 8](#).

8.2.2 Tumor Assessment Criteria

Radiographic tumor assessments, CT, or MRI scans should be performed according to the schedule in the SoA ([Section 1.3](#)), irrespective of whether study drug is delayed or missed. Brain scans (if CNS metastases are suspected) and bone scans will be performed at baseline according to the SoA. Analysis of tumor assessments for this study will be by Investigator assessment and will be collected on the eCRF.

8.2.3 Survival Assessment

Patients will continue to be followed to assess for survival status. Survival follow-up will occur every 3 months from EOT/Follow-up visit (whichever occurred later) until death, lost to follow-up, or withdrawal of consent, as outlined in the SoA ([Section 1.3](#)). Survival follow-up may be performed by phone contact or office visit.

8.3 Adverse Events

The definitions of an AE or SAE can be found in [Appendix 4](#).

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue the study drug or the study (see [Section 7.0](#)).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until 30 days after last dose given and at all time points specified in the SoA ([Section 1.3](#)). If the patient begins a new anticancer therapy, the period for recording non serious AEs on the eCRF ends at the time the new treatment is started. However, any SAEs related to study treatment occurring during the active collection period must still be reported to the Sponsor or designee and recorded in the eCRF, irrespective of any intervening treatment.

All AEs that begin before the start of study treatment but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of becoming aware of the event, as indicated in [Appendix 4](#). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in [Appendix 4](#).

8.3.2 Method of Detecting AEs and SAEs

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

If a patient is not able to provide valid verbal responses to open-ended questions another method of detecting AEs and SAEs will be applied per the Investigator's discretion.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in [Section 7.3](#)).

Further information on follow-up procedures is given in [Appendix 4](#).

8.3.4 Regulatory Reporting Requirements for SAEs

Reporting of SAEs by the sites will be managed on behalf of the Sponsor by ICON. Full details of the procedures to be adopted will be documented in a safety management plan approved by responsible parties. In brief:

All SAEs that occur within 30 days following the last dose of treatment with study medication, whether considered related to study medication or not, must be reported. All patients with SAEs must be followed-up for outcome.

Investigators should record all case details that can be gathered immediately (ie, within 24 hours after learning of the event) on the AE eCRF and submit the report via the electronic data capture (EDC) system.

In the event that the EDC system is unavailable, the paper SAE Form provided to Investigators should be completed and submitted to the Sponsor or its designee immediately (ie, no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to Investigators ([Appendix 4](#)). Once the electronic data capture (EDC) system is available, all information will be entered and submitted via the EDC system.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the

regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5 Pregnancy

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in the study. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in [Appendix 6](#). Patients who become pregnant will be discontinued from the study. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Pregnancy or elective abortion itself is not considered an AE unless there is a suspicion that investigational product may have interfered with the effectiveness of the contraceptive medication.

If a male patient's female partner is found to be pregnant while the patient is being treated or within 35 days of their last dose, the Investigator must submit the "pregnancy reporting and outcome form" through the SAE reporting process. The patient may continue in the study if an accidental pregnancy in the female partner occurs despite adequate contraception. Details of all pregnancies in female partners of male patients will be collected after the start of study drug and until 35 days after the last dose of study drug.

8.4 Treatment of Overdose

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

The Sponsor does not recommend any specific treatment for an overdose.

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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 patient.

There is no known antidote for palbociclib for overdose. General supportive measures should be taken (refer to palbociclib USPI).

8.5 Pharmacokinetics

As of Administrative Letter 5, PK sample collection is no longer required for active patients on Part A or Part C (including cohorts C1-C4 and C5). No patients remain on study treatment in Part B as of Protocol Amendment 6.

Blood sampling for PK analysis will be conducted as specified in [Table 5](#) (for Parts A and C, Cohorts C1-C4), [Table 6](#) (for Part C Cohort C5) and [Table 7](#) (for Part B).

8.5.1 Collection of Samples

Venous blood samples of approximately 1 mL will be collected for measurement of plasma concentrations of ARV-471 and ARV-473 (in all Parts), and palbociclib (in Part C) at times as specified in [Table 5](#) (for Parts A and C, Cohorts C1-C4), [Table 6](#) (for Part C, Cohort C5) and [Table 7](#) (for Part B). Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor. Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein.

The actual date and time (24-hour clock time) of each sample will be collected and recorded on the sample and in the eCRF.

The dose, actual date and time of the last dose of ARV-471 prior to blood sampling for PK will be recorded.

The dose, actual date and time of all doses of palbociclib in each cycle will be recorded. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

For patients with extensive PK sampling, pre-dose samples may be collected within 1 hour prior to dose administration. A 6-minute window will be allowed for samples taken up to 1 hour post-dose; a 15-minute window will be allowed for all additional samples taken post-dose (2, 4, 6, 8, and 12 [optional] hours).

8.5.2 Determination of Drug Concentration

Samples for the determination of ARV-471 and ARV-473 (in all Parts), and palbociclib (in Part C) in plasma will be analyzed on behalf of the Sponsor using appropriate validated chiral bioanalytical methods. Full details of the bioanalytical methods will be described in a separate bioanalytical report.

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

Remaining plasma samples may be subjected to further analysis by the Sponsor or designee to measure concentrations of selected co-administered medications, 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 (in all Parts), and

palbociclib (in Part C) may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

At visits during which blood samples for the determination of multiple aspects of study treatment will be taken, 1 sample of sufficient volume can be used.

Samples collected for concentration analyses of ARV-471 and its epimer ARV-473 or palbociclib may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

8.5.3 Calculation of Pharmacokinetic Variables

For patients with extensive PK sampling (Parts A and C) and if data allow, PK parameters on extensive PK sampling dates will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 8.1 or above (Certara, L.P. Princeton, New Jersey, United States of America [USA]) and/or SAS® Version 9.4 or above (SAS Institute, Inc., Cary, North Carolina, USA). Actual elapsed time from dosing will be used for the final plasma PK parameter calculations. For QD dosing, plasma concentrations 24 hours post-dose on Day 15 for Parts A and C will be assumed to be the same as the observed pre-dose plasma concentrations on Day 15 for the purpose of calculating PK parameters. For BID dosing, plasma concentrations 12 hours post-dose on Day 15 for Parts A and C will be assumed to be the same as the observed pre-dose plasma concentrations on Day 15 for the purpose of calculating PK parameters.

For patients with sparse PK sampling (Part B), population PK analysis approach (including PK data from both Parts A and B subjects) will be used to determine exposure and clearance parameter values for individuals. The effects of concomitant medications, patient demographics (eg, race, age, body size), and intrinsic factors such as renal or hepatic functions on the PK of ARV-471 and ARV-473 will be explored.

The PK parameters in [Table 21](#) will be determined for plasma ARV-471, ARV-473, and palbociclib, if data allow.

Table 21 Plasma Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
(Observed and dose-normalized) $C_{\max}$	Maximum concentration obtained directly from the observed concentration versus time data.
$T_{\max}$	Time to $C_{\max}$.
(Observed and dose-normalized) $C_{\min}$	Minimum concentration obtained directly from the observed concentration versus time data.
(Observed and dose-normalized) $AUC_{(0-\text{last})}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
(Observed and dose-normalized) $AUC_{(0-\text{tau})}$	Area under the plasma concentration-time curve during a dosing interval, calculated by linear up/log down trapezoidal summation.
CL/F	Apparent oral plasma clearance (parent only).
Vd/F at steady state	Apparent volume of distribution at steady state (parent only).
$RAUC_{(0-\text{tau})}$	Accumulation ratio for $AUC_{0-\text{tau}}$.
Effective $T_{1/2}$	Effective half-life based on accumulation ratio of $RAUC_{(0-\text{tau})}$.
$MRC_{\max}$	ARV-473 to ARV-471 ratio for $C_{\max}$.
$MRAUC_{(0-\text{tau})}$	ARV-473 to ARV-471 ratio for $AUC_{0-\text{tau}}$.
FI	Fluctuation index, defined as $(C_{\max\text{ss}} - C_{\min\text{ss}}) / C_{\text{avg}}$, where $C_{\text{avg}} = AUC_{0-\text{tau}, \text{ss}} / \text{tau}$.

8.6 Pharmacodynamics & Biomarkers

As of Administrative Letter 6, ctDNA sample collection is no longer required for active patients on Part A or Part C (including Cohorts C1-C4 and C5). No patients remain on treatment in Part B as of Protocol Amendment 6.

Samples for PD and biomarker research that should be collected from patients in the study are the following:

- Whole blood
- Tumor biopsy
- Plasma

Tissue samples will be tested by immunohistochemistry (IHC) for pertinent PD and biomarkers related to disease, including ER degradation, PR and Ki-67 levels, and ESR1 mutational status if

sufficient tissue is available. Additionally, historical ESR1 mutational status will be collected at baseline if available. Circulating tumor deoxyribonucleic acid (ctDNA) isolated from plasma will be used to determine ESR1 mutational status. In addition, samples will be stored, and analysis may be performed on PD and biomarker variants thought to play a role in breast cancer or drug response including, but not limited to, specific candidate genes/genome-wide analysis, or tissue biomarkers to evaluate their association with observed clinical responses to ARV-471. These samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to breast cancer and/or mechanism of action of the study drug. Tumor markers (CA 15-3, CA 27.29, CEA) will be assessed using a local laboratory. Samples may be stored for a maximum of 10 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to ARV-471.

8.7 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analyses Overview

The objectives of this study are to evaluate the safety and tolerability of ARV-471 and to determine the MTD and the RP2D as single agent and in combination with palbociclib. In Parts A and B of this study, ARV-471 treatment will be administered orally as repeated doses over 28 days per cycle among patients with ER+/HER2- locally advanced or mBC. In Part C, Cohorts C1-C4, ARV-471 treatment will be administered orally as repeated doses over 28 days per cycle and palbociclib treatment will be administered orally as repeated doses over 21 days followed by 7 days off over 28 days per cycle among patients with ER+/HER2- locally advanced or mBC. In Part C, Cohort C5, Cycle 1, palbociclib 100 mg will be given alone for 8 days (C1D1 through C1D8), prior to starting ARV-471 200 mg QD on Cycle 1 Day 9. Palbociclib 100 mg QD will begin on C1D1 and be given for 21 days followed by 7 days off treatment. In Cycles 2 and beyond, patients will receive, starting on Day 1, ARV-471 200 mg QD continuously and palbociclib 100 mg QD for 21 days followed by 7 days off-treatment.

Dose escalation and cohort expansion will be based on review of the available safety and PK data by the CRC (see [Section 10](#)).

A Statistical Analysis Plan (SAP) will be written to detail the analysis of all clinical, safety, and laboratory data collected for the study. The SAP will contain analysis of data from the Part A – Phase 1 Dose Escalation, Part B – Phase 2 Cohort Expansion, and Part C – Phase 1b Combination ARV-471 + palbociclib. Data from the dose escalation phases (Parts A and C) will be adequately summarized and reviewed by the CRC, prior to initiating a cohort expansion.

Unless otherwise noted, the statistical analyses presented below are applicable to the Part A – Phase 1 Dose Escalation, Part B – Phase 2 Cohort Expansion, and Part C – Phase 1b Combination ARV-471 + palbociclib. Patients from Part A who received the same dosing regimen as the RP2D may also be included in the analyses for Part B. If one or more doses are included in Part B – Phase 2 Cohort Expansion, sequential patients may be enrolled to each cohort in an alternating fashion. All analyses will be performed by treatment group without statistical comparisons made across treatment groups.

Descriptive statistics will be used to display the dose escalation data and results. Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a category. Time-to-event data will be plotted using the Kaplan-Meier method. The ORR, CBR, and DCR and corresponding 95% CIs will be calculated using the Clopper-Pearson method.

The statistical analysis will be performed using SAS Version 9.4 or above. The final tables, listings, and figures as well as clinical study report will be prepared after data is locked. Any deviations from the planned analysis will be described in the final study report.

9.2 Sample Size Determination

Part A: It is anticipated that 4 to 8 dose-escalation levels may be required to determine the MTD, and that at least 1 cohort will be expanded up to a total of 20 patients to allow for further characterization of the safety of ARV-471 as well as its PK/pharmacodynamic profile. Therefore, approximately 100 patients will be enrolled in the dose-escalation portion of this study.

Part B: Approximately 60 patients will be enrolled in two ARV-471 monotherapy cohorts (each enrolling 30 patients). A sample size of 60 patients in the efficacy analysis set will provide estimation of the CBR with 95% CI width 24.4% (or 34.7% for each cohort), if the observed response rate is 30% (ie, the 95% CI based on Clopper-Pearson method for the CBR will be estimated as 18.8%,43.2%). Corresponding 95% CI widths for other potentially observed CBR are provided in [Table 22](#) below. As a reference, the CBR reported for fulvestrant in the post-CDK 4/6 setting has been <20% ([Juric et al., 2018, 2019](#)).

Table 22 Clinical Benefit Rates and 95% CI per Clopper-Pearson method for the Part B – Phase 2 Cohort Expansion (N=60)

Number of Observed CBRs	CBR Rate	95% CI lower limit	95% CI upper limit
15	0.25	0.147	0.379
18	0.30	0.188	0.432
21	0.35	0.231	0.484
24	0.40	0.276	0.535
27	0.45	0.321	0.584
30	0.50	0.368	0.632

Abbreviations: CBR=clinical benefit rate; CI=confidence interval.

The sample size of 60 patients in the expansion cohort in the efficacy analysis set will provide estimation of the ORR to have a 95% CI width of 16.8%, if the observed response rate is 10%, ie, the 95% CI for the response rate will be estimated as (3.8%, 20.5%). Corresponding 95% CI widths for other potentially observed response rates are provided in [Table 23](#) below.

Table 23 ORR Rates and 95% CI per Clopper-Pearson method for the Part B – Phase 2 Cohort Expansion (N=60)

Number of Observed Responders	ORR	95% CI Lower Limit	95% CI Upper Limit
3	0.05	0.01	0.139
6	0.100	0.038	0.205
9	0.150	0.071	0.266
12	0.200	0.108	0.323
15	0.250	0.147	0.379
16	0.457	0.288	0.634
18	0.514	0.340	0.686

Abbreviations: CI=confidence interval; ORR=overall response rate.

Part C: It is anticipated that approximately 6-12 evaluable patients will be enrolled in a dose escalation in combination with palbociclib (Cohorts C1 and C2), followed by approximately 40 evaluable patients (approximately 20 each in Cohorts C3 and C4) treated in an expansion phase, and up to 16 patients to obtain a minimum of 8 PK evaluable patients in Cohort C5. Additional patients may be enrolled in Cohort C5 at the discretion of the sponsor to replace

patients who are not considered PK evaluable. Therefore, approximately 60 patients will be enrolled in Part C (combination) of this study, when the full cohort of patients is included.

For Cohort C5, assuming the within-subject standard deviations of 0.103 for $\ln AUC_{0-\tau}$ and 0.149 for $\ln C_{\max}$ of palbociclib, a sample size of 8 PK evaluable subjects will provide 90% CI of half width of 0.128 and 0.185 on the natural log scale for the estimated effect for palbociclib $AUC_{0-\tau}$ and $C_{\max}$ respectively with 90% coverage probability.

The following table presents the width of 90% CI (original scale) for different estimated effects based on sample size of 8 PK evaluable subjects.

Table 23 90% Confidence Interval for Different Estimated Effects Based on N = 8 PK Evaluable Patients (Part C Cohort C5)

Cohort 5 N = 8	Estimated effect (100*Combo/Mono)	90% CI		CI width
		Lower limit	Upper limit	
$AUC_{0-\tau}$	100%	0.8800	1.1364	0.2564
	125%	1.1000	1.4205	0.3205
	150%	1.3200	1.7046	0.3846
	175%	1.5400	1.9887	0.4487
	200%	1.7600	2.2727	0.5128
$C_{\max}$	100%	0.8312	1.2031	0.3720
	125%	1.0389	1.5039	0.4650
	150%	1.2467	1.8047	0.5580
	175%	1.4545	2.1055	0.6510
	200%	1.6623	2.4063	0.7440

$AUC_{0-\tau}$ = area under the plasma concentration-time curve during a dosing interval, calculated by linear up/log down trapezoidal summation; CI = confidence interval; $C_{\max}$ = maximum plasma concentration

9.3 Populations for Analyses

9.3.1 Enrolled Analysis Set

The enrolled analysis set consists of patients who are registered to participate in this study with informed consent signed and have successfully undergone the inclusion/exclusion criteria assessment.

9.3.2 Safety Analysis Set

The safety analysis set (also called the all treated population) consists of enrolled, ie, patients receiving any amount of ARV-471 dose (partial or complete) for monotherapy cohorts or any study drug for combination therapy cohorts. Safety analysis set will be used for the summary of

demographic and baseline characteristics, medical history and pre-existing conditions of patients, AEs, and laboratory results.

9.3.3 Dose-limiting Toxicity Analysis Set

The DLT analysis set is defined for Part A and Part C patients. Patients in Part A who were enrolled into the dose level that has already been cleared for dose escalation, ie, backfill patients, are excluded from the DLT analysis set. Patients in Cohort C3 and Cohort C4 are also excluded from the DLT analysis set. For Part A, the DLT analysis set includes all patients in Part A who receive at least 80% of their planned dose of ARV-471 in Cycle 1, and all patients who receive less than 80% of their planned dose of ARV-471 in Cycle 1 who had a DLT. For Part C the DLT analysis set includes all patients who receive at least 70% of planned doses of both palbociclib and ARV-471 in Cycle 1, and all who received less than 70% of planned doses in Cycle 1 who had a DLT.

9.3.4 Pharmacokinetic Analysis Set

The PK analysis set includes all ARV-471- and/or palbociclib-treated patients who have at least 1 plasma concentration-time data obtained (see the list in [Section 8.5.3](#)).

For Part C Cohort C5, PK evaluable patients are those patients who complete both C1D8 and Cycle 1 Day 21 (C1D21) intensive PK for palbociclib, and in whom both ARV-471 and palbociclib are considered to reach steady state at C1D8 and C1D21 at the discretion of the sponsor.

9.3.5 Response Evaluable Analysis Set

The response evaluable analysis set will be composed of all treated patients in the safety analysis set with baseline and at least 1 post-baseline radiographic assessment (CT/MRI scan). The response evaluable analysis set will be used for the summary of best overall response and tumor burden change from baseline analysis. Sensitivity analyses of all treated subjects will be performed for best overall response summary. The ORR analysis will be limited to patients with measurable disease by RECIST 1.1. DOR analysis will be limited to responders. The CBR evaluable analysis set includes all treated subjects who are enrolled at least 24 weeks prior to the data cutoff of analysis. The CBR evaluable analysis set will be used for the summary of CBR. Other efficacy parameters such as PFS and OS will be evaluated separately for all treated patients. Specific analyses by dose cohort and overall will be further described in the SAP (also see [Section 9.4.4.1](#)).

9.4 Statistical Analyses

The SAP will be developed and finalized prior to final analysis and will describe the patient analysis sets to be included in 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.

9.4.1 Patient Disposition

The study disposition of every enrolled patient will be presented by cohorts. Disposition will include the number of patients enrolled, number of patients who were treated, and the number of patients who discontinued study treatment early with reasons.

9.4.2 Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize the demographic and baseline variables for each dose cohort and for all patients combined. Demographic and baseline variables include age, ethnic origin, height, weight, and body mass index. Other baseline information includes medical and surgical history, prior and concomitant medications, and other disease factors.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (version March 2018 or later) and summarized by drug name and Anatomic Therapeutic Chemical (ATC) classification.

9.4.3 Safety Analyses

All safety analyses will be performed on the safety analysis set.

Safety data include TEAEs, vital signs, ECGs, PEs, and clinical laboratory assessments. A TEAE is an AE occurring on/after the date of first dose and within 30 days of the last dose of study drug (ARV-471 or palbociclib).

9.4.3.1 Adverse Events and Serious Adverse Events

All AEs recorded in the eCRFs will be coded using MedDRA (version 20.1 or higher) and graded using NCI CTCAE version 5.0. TEAE will be summarized by system organ class, preferred term, and/or maximum CTCAE grade in each treatment cohort, including number and percentage of patients with TEAEs, serious TEAEs, TEAEs that lead to discontinuation, and TEAEs that lead to death.

Causality of TEAEs being considered as “Probably related” or “Possibly related” by Principal Investigators will be defined as treatment-related. The treatment-related TEAEs and serious TEAEs will be summarized.

The number and percentage of patients with DLTs will be reported for each dose cohort using DLT population. The details of DLT will be listed.

9.4.3.2 Laboratory Tests

The absolute values and change from baseline of each parameter in hematology, blood chemistry, and coagulation will be summarized with n, mean, standard deviation, median, minimum and maximum values by visit. The shift of the post-baseline toxicity grade from baseline will be tabulated by visit. The shift of the worst post-baseline toxicity grade from baseline will be summarized as well.

The number and percentage of patients with elevated AST, ALT, total bilirubin, and alkaline phosphatase will be summarized in the safety analysis set. Elevations will be summarized as a function of the ULN.

- 3× ULN, 5× ULN, 10× ULN, and 20× ULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated total bilirubin to >2× ULN.
- Any elevations of ALP >1.5× ULN.
- Elevation of ALT/AST (>3× ULN) accompanied by elevated bilirubin (>1.5× ULN, >2× ULN).

9.4.3.3 Vital Signs

Vitals signs (eg, weight, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and body temperature) will be summarized by visit.

- Change from baseline by visit (including mean, median, standard deviation, maximum, and minimum)
- Percentage change from baseline at each visit through treatment discontinuation

9.4.3.4 Echocardiogram

If on-treatment echocardiograms are obtained, any changes in the ejection fraction and valvular structure and function will be summarized numerically and categorically using the safety analysis set.

9.4.3.5 Physical Examination

All PE results will be listed.

9.4.4 Efficacy Analyses

Efficacy analyses will be performed using the corresponding analysis set. The RECIST 1.1 criteria are available in [Appendix 8](#).

9.4.4.1 Best Response and Overall Response Rate

CT or MRI scans will be done every 8 weeks (±5 days) for the first 24 weeks of study treatment, then every 12 weeks (±5 days) thereafter, until discontinuation of study treatment. RECIST 1.1 will be used to determine each patient's visit response according to target lesion, non-target lesion and new lesion. The visit response categories include complete response (CR), PR, stable disease (SD), progressive disease, and NE. The patient best response will be determined according to all visit response by the following sequential: CR, PR, SD, progressive disease, and NE. The best response will be summarized by cohort.

The ORR is defined as the percentage of patients with a best overall response of CR or PR with the number of patients in the efficacy analysis set with measurable disease as the denominator. Patients with confirmed and unconfirmed responses will be included as responders. The ORR and its exact 95% CI will be summarized using Clopper-Pearson methodology.

The best percent change of the sum of target lesions from baseline, defined as the maximum decrease/or minimum increase of each patient, will be presented in a waterfall plot.

The disease control rate (DCR) is defined as the percentage of patients with a best overall response of CR, PR or SD with the number of patients in the efficacy analysis set as the denominator.

The CBR is defined as summation of CR, PR or SD of 24 weeks duration or longer. CBR evaluable patients will be included in the denominator. The CBR and its exact 95% CI will be summarized using the Clopper-Pearson methodology.

9.4.4.2 Time to Event

Duration of Response

DOR is the time interval from the date of first documented CR/PR to the date of disease progression (RECIST 1.1 progression) or death, whichever occurs first. DOR will be presented in a Kaplan-Meier plot in patients who had a best overall response of CR or PR.

Radiographic Progression-free Survival

Radiographic PFS is the time interval from the date of first study dose to the date of disease progression (RECIST 1.1 progression), or death, whichever occurs first. PFS data will be presented in a Kaplan-Meier plot for treated subjects.

Overall Survival

OS is the time interval from the date of first study dose to the date of death due to any cause. A patient who is alive will be censored on the date the patient was last known to be alive.

9.4.5 Pharmacokinetic Analyses

If data allow, non-compartmental and/or population PK methods will be used to calculate observed and dose-normalized PK parameters from ARV-471 and ARV-473 (in all Parts), and palbociclib (in Part C) plasma concentration-time data.

The PK parameters in [Table 21](#) will be calculated if data allow. Additional parameters may be calculated and reported when supported by the data. For selected PK parameters (eg, $AUC_{0-\tau}$), the value after repeated daily dosing will be compared to the corresponding value on Day 1 to evaluate accumulation of ARV-471, ARV-473, and palbociclib in plasma. For each patient, the concentration of ARV-471, ARV-473, and palbociclib in pre-dose (trough) samples will be used to measure the approach to steady state. See [Section 8.5.3](#).

The effect of ARV-471 on palbociclib PK will be evaluated using a linear mixed effect model. Geometric mean ratios and their 90% confidence intervals of steady state palbociclib C_{max} and $AUC_{0-\tau}$ will be estimated when palbociclib is given as a monotherapy and when given in combination with ARV-471 in Part C Cohort C5.

Descriptive statistics (including number, mean and/or median, standard deviation, coefficient of variation [CV], and range) for plasma concentrations by dose, date, and nominal time of sampling and PK parameters will be tabulated by dose level and days.

Mean linear and semi-logarithmic plots of the arithmetic mean plasma concentrations and standard deviation by scheduled sampling times will be provided by treatment. Linear and semilogarithmic spaghetti plots of the individual plasma concentrations by nominal sampling times will be provided by treatment and days.

In the expansion phase (including concentration-time data from both Parts A and B), exposure and clearance of ARV-471 and ARV-473 will be determined from sparse sampling using a population PK approach if data allow. Exposures from certain dose levels across Parts A and C will be compared to evaluate any DDI effect of palbociclib on ARV-471 PK. When appropriate, these data may also be combined with data from other studies as part of a meta-analysis. The results of population PK analysis will be reported separately.

9.4.6 Other Analyses

Additional exploratory biomarker analyses in ctDNA, and tumor tissue will be analyzed in a separate plan if sufficient data are available.

10. SAFETY MONITORING

10.1 Part A – Phase 1 Dose Escalation: Cohort Review Committee

The CRC membership, at a minimum, will be composed of the Principal Investigators/ Sub-Investigator designees from each clinical study site (one of which is considered to be a specialist with expertise in oncology), a Sponsor representative(s) including the Medical Monitor, a pharmacovigilance representative, and a statistician. Additional members may be added to the CRC, as appropriate.

The CRC 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.

A CRC will be established to review safety and PK data (as appropriate) from patients enrolled into the Phase 1 Dose Escalation. The CRC is responsible for reviewing and evaluating unblinded safety data after each cohort has completed 28 days of treatment (Cycle 1) and subsequently at regularly scheduled meetings as outlined in the cohort review meeting guidelines. PK data will also be considered by the CRC as appropriate. The CRC will also be responsible for the initiation of enrollment to the next dose level and determination of the dose to be tested at each of the next dose levels.

The CRC will recommend, and the Sponsor's CMO will approve, the RP2D selected for Part B, from one or more doses evaluated in Part A – Phase 1 Dose Escalation. Additional patients (up to 20 total per dose) may be added to a previously studied cohort once the Center for Disease Control (CDC) has deemed the dose to be safe. These additional patients are required to have measurable disease as per RECIST 1.1 at baseline and agree to have pre- and post-treatment core biopsies which will allow for further characterization of the safety of ARV-471 as well as its PK/PD profile. Additional details will be provided in the CRC guidelines.

All safety and PK data (as appropriate) will be reviewed by the CRC, which may decide to:

- Recommend dose escalation continues as planned (no DLT).
- Expand cohort to meet 3+3 rule if 1 DLT is observed in the first 3 patients entered. If no additional DLTs are observed in the additional 3 patients, the dose escalation will continue as described in [Section 4.4.1.1](#).
- Permanently stop enrollment in higher dose level cohorts and declare the dose level to be above MTD if 2 or more DLTs are identified in a cohort of 6 patients. In this case, all patients enrolled at the dose deemed to exceed the MTD will be dose reduced to the next lowest safe dose as determined by the CRC.
- Stop the study.

10.2 Part B – Phase 2 Cohort Expansion: Safety Review Committee

Once the MTD and/or RP2D have been determined by the CRC, and approved by the Sponsor's CMO, patients will receive ARV-471 orally at the RP2D or other recommended dose as determined from review of data. A Safety Review Committee (SRC) will be established to review the safety and PK data from patients enrolled into Part B – Phase 2 Cohort Expansion. The SRC will be formed prior to the enrollment of the first patient in the Part B – Phase 2 Cohort Expansion. The SRC will be composed of Sponsor's personnel responsible for the execution and safety oversight of this clinical trial as well as selected Principal Investigators. The SRC will be responsible for monitoring the ongoing safety data of patients enrolled in the cohort expansion on a quarterly basis beginning with the enrollment of the first patient in Part B and ending when all patients have completed study drug treatment or final database lock occurs.

Additional details will be provided in the SRC guidelines.

10.3 Part C – Phase 1b: Cohort Review Committee

Part C- Phase 1b combination: The CRC established in Part A will comprise the committee for Part C. They will review safety and PK data (as appropriate) from patients enrolled into the Phase 1b Dose Escalation. The CRC membership, at a minimum, will be composed of at least 4 Principal Investigators/Sub-Investigator designees, one of whom is considered to be a specialist with expertise in oncology, a Sponsor representative(s), a pharmacovigilance representative, and a statistician. Additional members may be added to the CRC as appropriate. The CRC is responsible for reviewing and evaluating safety data after each cohort has completed 28 days of treatment (Cycle 1) and subsequently at regularly scheduled meetings as outlined in the cohort review meeting guidelines. The CRC 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 CRC will also be responsible for the initiation of enrollment to the next dose level and confirmation of escalation to the next approved dose level. The CRC will recommend, and the Sponsor's CMO will approve, the doses of ARV-471 to be used in combination with palbociclib in the expanded portion of the Phase 1b. Patient safety will be monitored by the SRC established in Part B (see ARV-471 IB).

11. REFERENCES

- Agrawal, A., Robertson, J. F., Cheung, K. L., Gutteridge, E., Ellis, I. O., Nicholson, R. I., & Gee, J. M. (2016). Biological effects of fulvestrant on estrogen receptor positive human breast cancer: short, medium and long-term effects based on sequential biopsies. *International Journal of Cancer*, 138(1), 146–159. <https://doi.org/10.1002/ijc.29682>
- American Cancer Society Facts & Figures (2020). <https://www.cancer.org/content/dam/cancer-org/research/cancerfacts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf>
- Asghar, U., Witkiewicz, A. K., Turner, N. C., & Knudsen, E. S. (2015). The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nature Reviews. Drug Discovery*, 14(2), 130–146. <https://doi.org/10.1038/nrd4504>
- Astra Zeneca (2020). Faslodex (fulvestrant) injection, for intramuscular use: Full Prescribing Information [Report]. Astra Zeneca, revised 07/2020. [https://medicalinformation.astrazeneca-us.com/home/prescribinginformation/faslodexpi.html#:~:text=The%20recommended%20dose%20of%20FASLODEX,Clinical%20Studies%20\(14\)%5D](https://medicalinformation.astrazeneca-us.com/home/prescribinginformation/faslodexpi.html#:~:text=The%20recommended%20dose%20of%20FASLODEX,Clinical%20Studies%20(14)%5D)
- Barkhem, T., Carlsson, B., Nilsson, Y., Enmark, E., Gustafsson, J., & Nilsson, S. (1998). Differential response of estrogen receptor alpha and estrogen receptor beta to partial estrogen agonists/antagonists. *Molecular Pharmacology*, 54(1), 105–112. <https://doi.org/10.1124/mol.54.1.105>
- Bryant, H. U., Glasebrook, A. L., Yang, N. N., & Sato, M. (1999). An estrogen receptor basis for raloxifene action in bone. *The Journal of Steroid Biochemistry and Molecular Biology*, 69(1-6), 37–44. [https://doi.org/10.1016/s09600760\(98\)00147-2](https://doi.org/10.1016/s09600760(98)00147-2)
- Cristofanilli, M., Turner, N. C., Bondarenko, I., Ro, J., Im, S. A., Masuda, N., Colleoni, M., DeMichele, A., Loi, S., Verma, S., Iwata, H., Harbeck, N., Zhang, K., Theall, K. P., Jiang, Y., Bartlett, C. H., Koehler, M., & Slamon, D. (2016). Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *The Lancet. Oncology*, 17(4), 425–439. [https://doi.org/10.1016/S1470-2045\(15\)00613-0](https://doi.org/10.1016/S1470-2045(15)00613-0)
- Donovan, K. A., An, J., Nowak, R. P., Yuan, J. C., Fink, E. C., Berry, B. C., Ebert, B. L., & Fischer, E. S. (2018). Thalidomide promotes degradation of SALL4, a transcription factor implicated in Duane Radial Ray syndrome. *eLife*, 7, e38430. <https://doi.org/10.7554/eLife.38430>
- Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., Rubinstein, L., Shankar, L., Dodd, L., Kaplan, R., Lacombe, D., & Verweij, J. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer*, 45(2), 228–247. <https://doi.org/10.1016/j.ejca.2008.10.026>
- Flanagan, J. J., Y Qian, Y., Gough, S. M., Andreoli, M., Bookbinder, M., Bradley, J., Rousseau, E., Willard, R., Crews, C. M., Crew, A. P., Taylor, I., & Houston, J. (2017). Identification of Oral Estrogen Receptor PROTAC Degradors for Breast Cancer. Presentation at the San Antonio Breast Cancer Symposium, December, 2017. <https://s3.us-east-1.amazonaws.com/arvinas-assets.investeddigital.com/scientific-publications/2017-SABCSposter.pdf>

Food and Drug Administration (FDA) Guidance for Industry. In vitro drug interaction studies – cytochrome P450 enzyme- and transporter-mediated drug interactions. January 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions>.

Hammond, M. E., Hayes, D. F., Dowsett, M., Allred, D. C., Hagerty, K. L., Badve, S., Fitzgibbons, P. L., Francis, G., Goldstein, N. S., Hayes, M., Hicks, D. G., Lester, S., Love, R., Mangu, P. B., McShane, L., Miller, K., Osborne, C. K., Paik, S., Perlmutter, J., Rhodes, A., ... Wolff, A. C. (2010). American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Journal of Clinical Oncology* 28(16), 2784–2795. <https://doi.org/10.1200/JCO.2009.25.6529>

ICH International Council for Harmonisation. Dose Selection for Carcinogenicity Studies of Pharmaceuticals [Report].(2009). <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s1cr2-dose-selectioncarcinogenicity-studies-pharmaceuticals>

Juric, D., Ciruelos, E. M., Rubovszky, G., Campone, M., Loibl, S., Rugo, H. S., Iwata, H., Conte, P., Mayer, I. A., Kaufman, B., Yamashita, T., Lu, Y-S., Inoue, K., Takahashi, M., Pápai, Z., Longin, A-S., Mills, D., Wilke, C., Miller, M., Babbar, N., & Andre, F. (2018). Phase 3 SOLAR-1 trial results. Presented at the San Antonio Breast Cancer Symposium. December 6, 2018.

Juric, D., Ciruelos, E., Rubovszky, G., Campone, M., Loibl, S., Rugo, H.S., Iwata, H., Conte, P., Mayer, I.A., Kaufman, B., Yamashita, T., Lu, Y-S., Inoue, K., Takahashi, M., Pápai, Z., Longin, A-S., Mills, D., Wilke, C., Sellami, D., & Andre, F. (2019). Abstract GS3-08: Alpelisib + fulvestrant for advanced breast cancer: Subgroup analyses from the phase III SOLAR-1 trial. *Cancer Research* 79(4 Supplement) GS3-08; DOI:10.1158/15387445.SABCS18-GS3-08

Kuiper, G. G., Enmark, E., Peltö-Huikko, M., Nilsson, S., & Gustafsson, J. A. (1996). Cloning of a novel receptor expressed in rat prostate and ovary. *Proceedings of the National Academy of Sciences of the United States of America*, 93(12), 5925–5930. <https://doi.org/10.1073/pnas.93.12.5925>

Mariotto, A. B., Etzioni, R., Hurlbert, M., Penberthy, L., & Mayer, M. (2017). Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. *Cancer Epidemiology, Biomarkers & Prevention*, 26(6), 809–815. <https://doi.org/10.1158/1055-9965.EPI-16-0889>

Martín de las Mulas, J., Ordás, J., Millán, M. Y., Chacón, F., De Lara, M., Espinosa de los Monteros, A., Reymundo, C., & Jover, A. (2004). Immunohistochemical expression of estrogen receptor beta in normal and tumoral canine mammary glands. *Veterinary Pathology*, 41(3), 269–272. <https://doi.org/10.1354/vp.41-3-269>

Miller, T. W., Rexer, B. N., Garrett, J. T., & Arteaga, C. L. (2011). Mutations in the phosphatidylinositol 3-kinase pathway: role in tumor progression and therapeutic implications in breast cancer. *Breast Cancer Research*, 13(6), 224. <https://doi.org/10.1186/bcr3039>

Musgrove, E. A., Caldon, C. E., Barraclough, J., Stone, A., & Sutherland, R. L. (2011). Cyclin D as a therapeutic target in cancer. *Nature Reviews Cancer*, 11(8), 558–572. <https://doi.org/10.1038/nrc3090>

Nie, R., Zhou, Q., Jassim, E., Saunders, P. T., & Hess, R. A. (2002). Differential expression of estrogen receptors alpha and beta in the reproductive tracts of adult male dogs and cats. *Biology of Reproduction*, 66(4), 1161–1168. <https://doi.org/10.1095/biolreprod66.4.1161>

- Robinson, D. R., Wu, Y. M., Vats, P., Su, F., Lonigro, R. J., Cao, X., Kalyana-Sundaram, S., Wang, R., Ning, Y., Hodges, L., Gursky, A., Siddiqui, J., Tomlins, S. A., Roychowdhury, S., Pienta, K. J., Kim, S. Y., Roberts, J. S., Rae, J. M., Van Poznak, C. H., Hayes, D. F., ... Chinnaiyan, A. M. (2013). Activating ESR1 mutations in hormone-resistant metastatic breast cancer. *Nature Genetics*, 45(12), 1446–1451. <https://doi.org/10.1038/ng.2823>
- Thangavel, C., Dean, J. L., Ertel, A., Knudsen, K. E., Aldaz, C. M., Witkiewicz, A. K., Clarke, R., & Knudsen, E. S. (2011). Therapeutically activating RB: reestablishing cell cycle control in endocrine therapy-resistant breast cancer. *Endocrine-Related Cancer*, 18(3), 333–345. <https://doi.org/10.1530/ERC-10-0262>
- Toy, W., Weir, H., Razavi, P., Lawson, M., Goeppert, A. U., Mazzola, A. M., Smith, A., Wilson, J., Morrow, C., Wong, W. L., De Stanchina, E., Carlson, K. E., Martin, T. S., Uddin, S., Li, Z., Fanning, S., Katzenellenbogen, J. A., Greene, G., Baselga, J., & Chandarlapaty, S. (2017). Activating *ESR1* Mutations Differentially Affect the Efficacy of ER Antagonists. *Cancer Discovery*, 7(3), 277–287. <https://doi.org/10.1158/2159-8290.CD-15-1523>
- Turner, N. C., Ro, J., André, F., Loi, S., Verma, S., Iwata, H., Harbeck, N., Loibl, S., Huang Bartlett, C., Zhang, K., Giorgetti, C., Randolph, S., Koehler, M., Cristofanilli, M., & PALOMA3 Study Group (2015). Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. *The New England Journal of Medicine*, 373(3), 209–219. <https://doi.org/10.1056/NEJMoa1505270>
- Turner, N. C., Slamon, D. J., Ro, J., Bondarenko, I., Im, S. A., Masuda, N., Colleoni, M., DeMichele, A., Loi, S., Verma, S., Iwata, H., Harbeck, N., Loibl, S., André, F., Puyana Theall, K., Huang, X., Giorgetti, C., Huang Bartlett, C., & Cristofanilli, M. (2018). Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. *The New England Journal of Medicine*, 379(20), 1926–1936. <https://doi.org/10.1056/NEJMoa1810527>
- Uhlén, M., Fagerberg, L., Hallström, B. M., Lindskog, C., Oksvold, P., Mardinoglu, A., Sivertsson, Å., Kampf, C., Sjöstedt, E., Asplund, A., Olsson, I., Edlund, K., Lundberg, E., Navani, S., Szgyarto, C. A., Odeberg, J., Djureinovic, D., Takanen, J. O., Hober, S., Alm, T., ... Pontén, F. (2015). Proteomics. Tissue-based map of the human proteome. *Science*, 347(6220), 1260419. <https://doi.org/10.1126/science.1260419>
- US FDA (2002). Drug Approval Package. Faslodex (Fulvestrant) Injection; Company: AstraZeneca Pharmaceuticals. (Application No.: 21-344; Approval Date: 4/25/2002). [Report]. - Rockville (MD) U.S. Food and Drug Administration (U.S. FDA), Center for Drug Evaluation and Research (CDER). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-344_FulvestrantFaslodex.cfm
- US FDA (2005). Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Guidance for Industry. US Department of Health and Human Services [Report]. Food and Drug Administration. Center for Drug Evaluation and Research. <https://www.fda.gov/regulatory-information/search-fdaguidance-documents/estimating-maximum-safe-starting-dose-initial-clinical-trials-therapeutics-adult-healthyvolunteers>
- Wakeling, A. E., Dukes, M., & Bowler, J. (1991). A potent specific pure antiestrogen with clinical potential. *Cancer Research*, 51(15), 3867–3873.
- Wolff, A. C., Hammond, M., Allison, K. H., Harvey, B. E., Mangu, P. B., Bartlett, J., Bilous, M., Ellis, I. O., Fitzgibbons, P., Hanna, W., Jenkins, R. B., Press, M. F., Spears, P. A., Vance, G. H., Viale, G., McShane, L. M., & Dowsett, M. (2018). Human Epidermal Growth Factor Receptor 2

Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Journal of Clinical Oncology*, 36(20), 2105–2122. <https://doi.org/10.1200/JCO.2018.77.8738>

Yu, Q., Sicinska, E., Geng, Y., Ahnström, M., Zagozdzon, A., Kong, Y., Gardner, H., Kiyokawa, H., Harris, L. N., Stål, O., & Sicinski, P. (2006). Requirement for CDK4 kinase function in breast cancer. *Cancer Cell*, 9(1), 23–32. <https://doi.org/10.1016/j.ccr.2005.12.012>

12. APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
%F	bioavailability
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AR	androgen receptor
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the plasma concentration-time curve
AUC ₀₋₂₄	AUC from time zero to 24 hours
AUC _{INF}	AUC from time zero to infinity
AUC _{0-last}	AUC from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
AUC _{0-tau}	AUC from time zero during a dosing interval, calculated by linear up/log down trapezoidal summation
AV	atrioventricular
BCRP	breast cancer resistance protein
BID	twice daily
CA	cancer antigen
CAP	College of American Pathologists
CBR	clinical benefit rate
CDC	Center for Disease Control
CDKi	CDK4/6 inhibitors
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent oral plasma clearance
C _{max}	maximum concentration, obtained directly from the observed concentration versus time data

Cmin	minimum concentration, obtained directly from the observed concentration versus time data
CMO	Chief Medical Officer
CNS	Central nervous system
CR	complete response
CRC	Cohort Review Committee
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CV	coefficient of variation
CYP	cytochrome P450 enzyme
DC ₅₀	half-maximal degradation concentration
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
Effective T _{1/2}	effective half-life based on accumulation ratio
EOT	End of Treatment
ER	estrogen receptor
ER+/HER2-	estrogen receptor positive/human epidermal growth factor receptor 2 negative
ESR1	estrogen receptor 1
FDA	Food and Drug Administration
FI	fluctuation index
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI ₅₀	half-maximal growth inhibition
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
GR	glucocorticoid receptor
GSPT1	G1 to S phase transition 1 gene
HED	human equivalent dose

HER2	human epidermal growth factor receptor 2
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HR	hormone receptor
IC ₅₀	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IM	intramuscular
IMiD	immunomodulatory imide drugs
INR	international normalized ratio
IRB	Institutional Review Board
LD	longest diameter
LLN	lower limit of normal
LPFV	last patient first visit
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mpk	mg per kg
MRAUC _{0-tau}	ARV-473 to ARV-471 ratio for AUC _{0-tau}
MRC _{max}	ARV-473 to ARV-471 ratio for C _{max}
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NE	not evaluable
NOAEL	no observed adverse effect level
ORR	overall response rate
OS	overall survival
PD	progressive disease
PE	physical examination
PFS	progression-free survival
PI	Principal Investigator
P-gp	P-glycoprotein
PK	pharmacokinetic(s)

PO	per oral
PR	partial response
PROTAC	PROteolysis-TArgeting Chimera
QD	once daily
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia's method
RAUC _{0-tau}	ARV-473 to ARV-471 ratio for AUC _{0-tau}
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SERD	selective estrogen receptor degrader/downregulator
SoA	Schedule of Activities
SRC	Safety Review Committee
STD10	severely toxic dose in 10% of rodents
SULT	sulfotransferase
T _½	terminal half-life of elimination
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
T _{max}	time to C _{max}
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
V _d /F	apparent volume of distribution
V _{ss}	volume of distribution
WOCBP	women of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

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 Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page ([Appendix 11](#)) 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.

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 1 year after completion of the study.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients 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 guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

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

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

Data Protection

Patients will be assigned a unique identifier by the Sponsor (or designee). Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient 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 patient.

The patient 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/IEC members, and by inspectors from regulatory authorities.

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The Sponsor or its representative will not provide individual genotype results to patients, 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 patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, the Sponsor or representative physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

The CRC/SRC will include, at a minimum, the Sponsor's responsible physician and the Principal Investigator from each investigative site. The Principal Investigator and the Sponsor, when appropriate, will invite other specialist individuals to participate in the review, eg, PK scientists, statisticians, clinical specialists, etc.

Table 24 presents the administrative structure.

Table 24 Study Administrative Structure

Function	Responsible Organization
Study Operations Management	ICON
Medical Monitoring	████████████████████
24-hour Medical Monitoring Coverage	████████████████
Study Master File	ICON
Data Management	ICON
Clinical Supply Management	Fisher Clinical Services
Quality Assurance Auditing	ICON
Biostatistics	ICON
Medical Writing	Arvinas, Inc. and ICON
Laboratory Assessments	Local laboratories; Foundation One for specialized testing (eg, circulating tumor cell DNA, Knight Diagnostics IHC)
Electrocardiogram Collection, Review, and Analysis	Local laboratories
Pharmacokinetic Sample Testing	Aliri (formerly Pyxant Labs Inc.) (for ARV-471) PPD Bioanalytical Lab (for palbociclib)
Management of Adverse Event Adjudication	ICON
Cohort Review Committee/Safety Review Committee	Arvinas, Inc. and ICON

Medical Monitor

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

24-hour Medical Monitoring Coverage

[REDACTED]
[REDACTED]

24-hour Safety Reporting

[REDACTED]
[REDACTED]

Fax: [REDACTED]

E-mail: [REDACTED]

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the appropriate database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons (where applicable).

Data Quality Assurance

All patient data relating to the study will be recorded in printed or eCRFs 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 eCRF.

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

The Investigator must permit related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

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

Records and documents, including signed ICFs, 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.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's patients. 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).

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.

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

Definition of what constitutes source data can be found in Clinical Monitoring Plan.

Study and Study Center Closure

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

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

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

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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. Sponsor will base its publication policy on a number of key factors that include intellectual input into the protocol design, analysis of data and patient enrollment. Sponsor is committed to a fair and equitable determination of the various publication roles such as lead author and senior author on future manuscripts and abstracts/presentations.

Appendix 3 Clinical Laboratory Tests

The tests detailed in [Table 25](#) 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.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in [Section 5](#) of the protocol.

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

Pregnancy Test Requirements

All women of childbearing potential require pregnancy testing according to the SoA ([Section 1.3](#)). Information on acceptable contraception methods for males and females is provided in [Appendix 6](#). Women considered to be not of childbearing potential are defined below.

- Postmenopausal status due to either surgical/natural menopause or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a GnRH agonist such as goserelin.
- Postmenopausal status due to surgical/natural menopause requires at least 1 of the following:
 - prior bilateral oophorectomy
 - age ≥ 60 years
 - age < 60 years and amenorrhoeic for at least 12 months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol levels in the postmenopausal range

Table 25 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet Count
	Red Blood Cell Count
	Hemoglobin
	Hematocrit
	<u>White Blood Cell Count with Differential:</u>
	Absolute Neutrophils
	Absolute Lymphocytes
	Absolute Monocytes
	Absolute Eosinophils
	Absolute Basophils
	White blood cells

Laboratory Assessments	Parameters	
Clinical Chemistry¹	Blood urea nitrogen (BUN)	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)
	Creatinine	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)
	Glucose (non-fasting)	Alkaline phosphatase (ALP)
	BUN or Urea	Creatine kinase
	Magnesium	Creatine kinase MB fraction will be performed if clinically indicated
	Potassium	Chloride
	Sodium	Amylase
	Total Calcium	Total bilirubin
	Lactate dehydrogenase	Direct, conjugated and unconjugated bilirubin will be performed if clinically indicated
	Albumin	Total protein
	Uric acid	Phosphorus or phosphate
Coagulation	International normalized ratio (INR)	Carbon dioxide (bicarbonate)
	Prothrombin time (PT)	
	Partial prothrombin time	
Urinalysis²	Leucocyte esterase	pH
	Protein	
	Urine Bilirubin	Nitrites
	Urobilinogen	Specific gravity
	Ketones	Glucose (qual)
	Microscopy ³ (if clinically indicated)	Blood (qual)
Viral serology	HIV I and II	Hepatitis C Virus
	HBsAg	
Thyroid profile	Thyroid stimulating hormone (TSH)	
Other tests	Pregnancy (serum at Screening; urine only on study); Tumor markers (CA 15-3, CA 27.29, CEA) ⁴	

Note: There is no need to repeat hematology, blood chemistry (with the exception of serum creatinine which must be performed within 72 hours of Cycle [C] 1 Day [D] 1), coagulation, and urinalysis on C1D1 if baseline assessment is performed within 72 hours prior to that date.

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in [Section 7.1](#).
2. Urine dipstick testing is acceptable at Screening and End of Treatment visit. At Screening, if dipstick shows urine protein ++ or above, perform 24-hour urine protein test and exclude patients whose 24-hour urine protein is $\geq 1\text{g}/24\text{ hours}$.
3. Only if urine dipstick is positive for blood, protein, nitrates or leukocyte esterase.
4. Tumor markers will be assessed at baseline. Only elevated markers will be followed on study and timing should coincide with radiographic assessments.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event (AE)

AE Definition
- An AE is any untoward medical occurrence in a patient or patient, temporally associated with the use of study drug, whether or not considered related to the study treatment. - 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 treatment.
Events <u>Meeting</u> the AE Definition
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to the progression of underlying disease). - Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. - New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. - Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. - Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. - New signs or symptoms or worsening in severity of a cancer symptom that occur in association with disease progression should be recorded as AEs.
Events <u>NOT</u> Meeting the AE Definition
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient'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 patient'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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event (SAE)

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term ‘life-threatening’ in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which 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 patient 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 pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person’s ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient 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.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording Following implementation of Protocol Amendment 6, only the following events must be recorded on the eCRF: • AEs leading to discontinuation of study drug ○ This includes clinically significant changes, in the opinion of the investigator, noted during standard of care safety assessments (physical exam, vital signs, ECOG, laboratory values, ECG evaluations, etc.) leading to discontinuation. • SAEs Note: Non-serious AEs, excluding the events listed above, will not be reported to the Sponsor in the eCRF, but will be recorded in site source documentation. The SAE reporting process remains unchanged. • When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately. • It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient 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/SAE.
Assessment of Intensity The Investigator will make an assessment of the intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
Assessment of Causality • The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated (unlikely related, not related) or related (possibly related, probably related, or related). ○ "Related" is used if the AE is clearly related to administration of the study treatment. ○ "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. ○ "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions. ○ "Unlikely related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE. ○ "Not related" is used if there is not a reasonable possibility that the study treatment caused the AE.

• The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/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 makes 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 a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory 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 health care professionals. • If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via Paper eCRF
The Investigator must report all SAEs within 24 hours of the Investigator's discovery to ICON safety team: Attention: [REDACTED] E-mail: [REDACTED] Fax number: Fax: [REDACTED] The ICON safety team will contact the Investigator via telephone for follow-up information regarding the SAE, as appropriate. 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.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

<https://evs.nci.nih.gov/ftp1/CTCAE/About.html>

Appendix 5 Definitions for Dose-limiting Toxicities, Maximum Tolerated Dose, and Recommended Phase 2 Dose

PART A:

Dose-limiting Toxicity (DLT)

Severity of AEs will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For dose escalation, any of the following AEs occurring within 28 days after the start of the study treatment which are attributable to ARV-471 and unrelated to mBC, intercurrent illness, or concomitant medications will be classified as DLTs.

All AEs of the specified grades should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

Hematologic DLTs

- Prolonged myelosuppression, defined as CTCAE Grade ≥ 3 hematologic parameters (ANC $< 1000/\text{mm}^3$, platelet count $< 50,000/\text{mm}^3$, or hemoglobin $< 8 \text{ g/dL}$) in a bone marrow with $< 5\%$ blasts and no evidence of leukemia or abnormal dysplasia, that lasts longer than 28 days from the point of detection.
- Grade ≥ 3 neutropenia with infection.
- Grade 4 neutropenia lasting > 5 days.
- Febrile neutropenia (defined as an ANC $< 1.0 \times 10^9/\text{L}$ with a single temperature of $> 38.3^\circ\text{C}$ or 101°F , or a sustained temperature of $\geq 38^\circ\text{C}$ or 100.4°F for more than 1 hour).
- Grade 3 thrombocytopenia with bleeding.
- Grade 4 thrombocytopenia.
- Any toxicity requiring dose interruption for ≥ 14 days will be considered a DLT.
- Grade 3 leukopenia or neutropenia less than 28 days unaccompanied by fever or infection will NOT be considered a DLT.
- Grade 3 thrombocytopenia of less than 28 days without clinical evidence of bleeding will NOT be considered a DLT.
- Anemia not requiring transfusion will NOT be considered a DLT.
- Any isolated Grade 3 lymphopenia of any duration will NOT be considered a DLT.

Non-hematologic DLTs

- Grade ≥ 3 toxicities that are considered clinically significant, except those that have not been maximally treated:
 - Grade 3 nausea/vomiting/diarrhea or Grade 4 vomiting/diarrhea lasting < 72 hours in the absence of maximal medical therapy are NOT considered a DLT.
 - Grade 3 fatigue lasting less than 7 days is NOT considered a DLT.

- Hy's Law (concomitant ALT or AST elevation of $\geq 3 \times \text{ULN}$ and total bilirubin elevation of $\geq 2 \times \text{ULN}$ without a clear alternative etiology) is considered a DLT.
- Grade ≥ 3 electrolyte abnormality that lasts >72 hours, unless the patient has clinical symptoms, in which case all Grade ≥ 3 electrolyte abnormality regardless of duration should count as a DLT.
- Grade ≥ 3 amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis is NOT considered a DLT.
- QT interval corrected using Fridericia's method (QTcF) prolongation: Any Grade ≥ 3 QT prolongation must be considered a DLT. The patient must also be evaluated by cardiology and discontinued from the study and study drug.
- Any AE attributed to ARV-471 requiring dose interruption for ≥ 14 days will be considered a DLT.
- Any death not clearly due to the underlying disease or extraneous causes.

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

Evaluable Patients for DLT Review

All patients in the dose escalation phase who have a DLT will be included as DLT-evaluable.

Patients in the dose escalation phase who fail to complete at least 80% of study drug treatment in Cycle 1 for reasons other than DLT (eg, logistical or technical reasons, non-DLT-related dose delays) are considered not to be DLT-evaluable and will be replaced, but they can remain on study and receive additional treatment with ARV-471 per protocol. Patients in the dose escalation phase who withdraw for any reason after Cycle 1 will not be replaced.

Maximum Tolerated Dose (MTD)

The MTD estimate is the highest dose associated with the occurrence of DLTs, as pre-specified in the DLT definition above, in $<33\%$ of DLT-evaluable patients.

In practice, the MTD estimate is the dose level at which 0/6 or 1/6 DLT-evaluable patients experience a DLT during the first treatment cycle(s) with the next higher dose having at least 2 of 3 to 6 DLT-evaluable patients experiencing DLTs.

Recommended Phase 2 Dose

The RP2D is the dose(s) chosen for further study based on the dose escalation study results in Part A. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D lower than the MTD.

PART C:**Definition for Dose-limiting Toxicities**

Severity of AEs will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For dose escalation, any of the following AEs occurring within 28 days after the start of the study treatment which are attributable to the study regimen and unrelated to mBC, intercurrent illness, or concomitant medications will be classified as DLTs.

All AEs of the specified grades should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

Hematologic Adverse Events:

Hematologic toxicities will not be considered a DLT for the combination of ARV-471 and palbociclib, but instead will be ascribed as related to palbociclib alone. Dose reduction/modification will follow the palbociclib prescribing information as outlined in [Section 4.4.2.2](#) and (Pfizer Inc., 2019).

Non-hematologic Adverse Events:

- Non-hematologic DLTs are Grade ≥ 3 toxicities that are considered clinically significant, except those that have not been maximally treated:
 - Grade 3 nausea/vomiting/diarrhea or Grade 4 vomiting/diarrhea lasting < 72 hours in the absence of maximal medical therapy are NOT considered a DLT.
 - Grade 3 fatigue lasting less than 7 days is NOT considered a DLT.
- Hy's Law (concomitant ALT or AST elevation of $\geq 3 \times \text{ULN}$ and total bilirubin elevation of $\geq 2 \times \text{ULN}$ without a clear alternative etiology) is considered a DLT.
- Grade ≥ 3 electrolyte abnormality that lasts > 72 hours, or any Grade ≥ 3 electrolyte abnormality associated with symptoms, regardless of duration, is considered a DLT.
- Grade ≥ 3 amylase or lipase elevation without associated symptoms or clinical manifestations of pancreatitis is NOT counted as a DLT.
- QT interval corrected using Fridericia's method (QTcF) prolongation: Any Grade ≥ 3 QT prolongation must be considered a DLT. The patient must also be evaluated by cardiology and discontinued from the study and study drug.
- Any AE attributed to ARV-471 requiring dose interruption for ≥ 14 days will be considered a DLT.
- Any death not clearly due to the underlying disease or extraneous causes.

Clinically important or persistent toxicities (eg, toxicities responsible for significant dose delay) that are not included in the above criteria may also be considered a DLT following review by the CRC in consultation with the Sponsor. To be considered a DLT, the AE must represent a clinically significant shift from baseline and must be considered at least likely related to the study drugs by the Investigator or Sponsor.

Evaluable Patients for DLT Review

All patients in the dose escalation phase who have a DLT will be included as DLT-evaluable. Patients in the dose escalation phase who fail to complete at least 70% of study drug treatments in Cycle 1 for reasons other than DLT (eg, logistical or technical reasons, non-DLT-related dose delays) are considered not to be DLT-evaluable and will be replaced, but they can remain on study and receive additional treatment with ARV-471 and/or palbociclib per protocol. Patients in the dose escalation phase who withdraw for any reason after Cycle 1 will not be replaced.

Maximum Tolerated Dose (MTD)

The MTD estimate is the highest dose associated with the occurrence of DLTs, as pre-specified in the DLT definition above, in <33% of DLT-evaluable patients.

Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

Female patients of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame and for at least 4 weeks after the last dose of study drug:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to have their male partner use a condom and agree to use a contraceptive method with a failure rate of <1% per year as described in [Table 26](#) when having penile-vaginal intercourse.

At the time of Protocol Amendment 6, all male patients received the last dose of study treatment more than 6 months prior to implementation of Protocol Amendment 6. The contraception and sperm donation guidance for male patients is no longer applicable.

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom and have their partner use a contraceptive method with a failure rate of <1% per year as described in [Table 26](#) when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male patients must refrain from donating sperm for the duration of the study and for 6 months after the last dose of study treatment.

Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for at least 35 days after the last dose of study drug.

Table 26 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent¹ <i>Failure rate of <1% per year when used consistently and correctly.</i>
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation ² • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent¹
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation² • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner <i>A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.</i>
Sexual abstinence <i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.</i>

1. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.
2. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 35 days after the last dose of study treatment.

Collection of Pregnancy Information

The Investigator will attempt to collect pregnancy information on any female who becomes pregnant while in this study. This applies only to patients who receive ARV-471.

After obtaining the necessary signed informed consent from the pregnant female directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy. The female patient will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Appendix 7 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, 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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and 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, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Appendix 8 RECIST 1.1

Response evaluation criteria in solid tumors: Revised RECIST criteria ([Eisenhauer et al., 2009](#)) are summarized below.

Measurable/Non-Measurable Lesions. Each tumor lesion or site of disease identified at baseline is categorized as either a measurable lesion or a non-measurable lesion according to the following definitions.

Lesion Type	Qualifying Definition
Measurable	Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT scan (CT scan slice thickness no greater than 5 mm.) • 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable) • 20 mm by chest X-ray. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability: bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of the treatment.

Target Lesions. Target lesions are selected from measurable lesions at baseline on the basis of their size and suitability for accurate repeated measurements by imaging techniques or clinical judgment. The sum of the longest diameter (LD) for all target lesions provides a quantitative means of characterizing objective tumor response to treatment as follows:

Evaluation Criteria Used for Categorizing Treatment Response of Target Lesions	
Response Category	Definition
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	>30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	>20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Non-Target Lesions. Non-target lesions are other lesions (or sites of disease) not identified as target lesions at baseline. These include both non-measurable lesions as well as measurable lesions exceeding the maximum number allowed per organ or in total. The response of nontarget lesions to treatment is evaluated on the basis of their presence or absence as follows:

Evaluation Criteria Used for Categorizing Treatment Response of Non-Target Lesions	
Response Category	Definition
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker levels initially above upper limits of normal
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

New Lesions. New lesions not present at baseline should be recorded at time of occurrence.

Overall Response. The overall response (OR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed after the criteria for response are first met (4-6 weeks later). In the case of SD, follow-up measurements must have met the SD criteria at least once with a minimum interval of at least 6-8 weeks from randomization.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR*
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD**
Any	PD	Yes or No	PD**
Any	Any	Yes	PD**

*When evaluation of possible CR depends on distinguishing residual disease from normal tissue, fine needle aspirate/biopsy is recommended before confirming the complete response status.

**Patients without objective evidence of disease progression, but with globally deteriorated health status requiring discontinuation of treatment should be classified as having “symptomatic deterioration” at that time, with every effort made to document the objective progression, even after discontinuation of treatment.

Duration of Response. The DOR is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started). SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Appendix 9 Examples of Sensitive P-gp Substrates and Those with Narrow Therapeutic Indices, Strong CYP3A4 Inhibitors and Inducers, Sensitive CYP2B6 Substrates and CYP2B6 Substrates with Narrow Therapeutic Indices, and Drugs with Known QT Risk

Participants should not receive the following while participating in trials with ARV-471.

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:

Sensitive P-gp substrates with narrow therapeutic indices:	dabigatran etexilate, digoxin, fexofenadine, apixaban, rivaroxaban
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- Examples of moderate and strong CYP3A4 inhibitors and inducers

Moderate CYP3A4 inhibitors:	dronedarone, ciprofloxacin, erythromycin, lefamulin, fluvoxamine, netupitant, aprepitant, fluconazole, isavuconazole, istradefylline, amprenavir, atazanavir, darunavir, letermovir, ritonavir, tofisopam, diltiazem, verapamil, cimetidine, schisandra sphenanthera, berotralstat, cyclosporine, voxelotor
Moderate CYP3A4 inducers:	semagacestat, nafcillin, rifabutin, cenobamate, phenobarbital, primidone, telotristat ethyl, lesinurad, thioridazine, asunaprevir and beclabuvir and daclatasvir, efavirenz, etravirine, lersivirine, lopinavir, talviraline, tipranavir and ritonavir, bosentan, elagolix, modafinil, metamizole
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 sensitive CYP2B6 substrates and CYP2B6 substrates with narrow therapeutic indices

Sensitive CYP2B6 substrates and CYP2B6 substrates with narrow therapeutic indices:	bupropion, efavirenz
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- 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 (dihydroquinidine), hydroxychloroquine, ibogaine, ibutilide, levofloxacin, levomepromazine (methotrimeprazine), levomethdil acetate, levosulpiride, meglumine antimoniate, mesoridazine, methadone, mobocertinib, 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>
 - o 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>
 - o Table 3-2: Examples of clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (03/06/2020)
 - o 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 sensitive CYP2B6 substrates and those with narrow therapeutic indices

- <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-tablesubstrates-inhibitors-and-inducers>
 - o Table 3-1: Examples of clinical substrates for P450-mediated metabolism [for concomitant use clinical DDI studies and/or drug labeling (12/03/2019)]

Examples of known QT prolonging drugs (12/13/2021)

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

Appendix 10 COVID-Related Guidelines

Please also refer to FDA Guidance: <https://www.fda.gov/media/136238/download>

Guidance for COVID Vaccine Administration

- **For participants who have not initiated study treatment:**

It is recommended that they should receive the second dose of vaccine at least 5 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.

- **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.

TeleMed Visit Guidance and Accepted Use

The use of Video TeleMed Visits during the COVID pandemic 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 15 of Cycle 2 and beyond may be done via TeleMed if the participant did not have any significant toxicities requiring re-assessment at the previous in-person Day 28 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.

Shipment of drug supply based on COVID-related limitations.

Participants who cannot be seen in clinic due to quarantine requirements or other limitations due to COVID restrictions 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 patient compliance and the need for direct shipment to the patient.

Positive COVID Test

If a participant currently on study treatment has a positive COVID test result, the treating Investigator should immediately hold study treatment and contact the Medical Monitor to discuss the case.

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 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.

Appendix 11 Signature of Investigator

PROTOCOL TITLE: A Phase 1/2, open label, dose escalation, and cohort expansion clinical trial to evaluate the safety, tolerability, and pharmacokinetics of ARV-471 alone and in combination with palbociclib (IBRANCE[®]) in patients with estrogen receptor positive/human epidermal growth factor receptor 2 negative (ER+/HER2-) locally advanced or metastatic breast cancer, who have received prior hormonal therapy and chemotherapy in the locally advanced/metastatic setting

PROTOCOL NO: ARV-471-mBC-101

VERSION: Amendment 6

This protocol is a confidential communication of Arvinas, 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, 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:

Signature Page for VV-CLIN-000483 v7.0

Approval	Clinical 19-Feb-2025 20:53:47 GMT+0000
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Signature Page for VV-CLIN-000483 v7.0