



# Statistical Analysis Plan

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 Version No./Date: | ARV-471-mBC-101, Amendment 5 / 13MAR2023                                                                                                                                                                                                                                                                                                                                                                                                                              |
| CRF Version No./Date:      | v10.0 / 22MAY2023                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| SAP Version No./Date:      | v3.0 / 26JAN2024                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

## 1.0 Approvals

|                          |               |
|--------------------------|---------------|
| Sponsor                  |               |
| Sponsor Name:            | Arvinas, Inc. |
| Representative/ Title:   | [REDACTED]    |
| Signature /Date:         |               |
| PRA                      |               |
| Biostatistician / Title: |               |
| Signature /Date:         |               |

(NOTE: Electronic Signature



## 2.0 Change History

| Version/Date     | Change Log                                                                                                                                                                                                                                                                                                                                              |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| v0.1 / 07AUG2020 | Created as initial draft, including incorporation of the Phase 2 Cohort Expansion.                                                                                                                                                                                                                                                                      |
| v0.2 / 30OCT2020 | Updates based on requirements for the 2020 End of Year Disclosure.                                                                                                                                                                                                                                                                                      |
| v0.3 / 14OCT2021 | Initial creation of TLF Shells, along with updates based on Protocol Amendment 3 and the SABCS requirements.                                                                                                                                                                                                                                            |
| v0.4 / 17JAN2022 | Updates based on Sponsor feedback to v0.3<br>Updates to the PK Sections based on Protocol Amendment 3.                                                                                                                                                                                                                                                  |
| v1.0 / 31JAN2022 | Updates based on Sponsor feedback to v0.4.<br>Redacted PK Analysis Section for finalization after Draft v1.0 approval.<br>Version rounded for approval of Draft SAP/Shells to enable Dry Run 1 production.                                                                                                                                              |
| v1.1 / 22FEB2022 | Added PK Sections.                                                                                                                                                                                                                                                                                                                                      |
| v2.0 / 01MAR2022 | Updates to PK Sections based on Sponsor feedback to v1.1.<br>Updates to ECG Section for windowing triplicate values.<br>Version rounded for approval of Draft SAP/Shells to continue with Dry Run 1 production.                                                                                                                                         |
| v2.1 / 02MAR2022 | Updated to PK Sections based on Sponsor feedback to v2.0.                                                                                                                                                                                                                                                                                               |
| v2.2 / 18MAY2022 | Updates to the Exploratory Analysis Section to include various subgroup analyses for CBR and PFS and to the Safety sections to include additional TEAE summaries as requested by the Sponsor.<br>Updates to PK Sections to explain the presentation of TLFs now based on Initial Dose.<br>Updates to incorporate changes based on Protocol Amendment 4. |
| v2.3 / 19DEC2023 | Updates to incorporate changes requested by Sponsor from Dry Run 1.<br>Updates to incorporate changes requested by Sponsor from Dry Run 2.<br>Updates to incorporate changes based on Protocol Amendment 5.                                                                                                                                             |
| v2.4 / 23JAN2024 | Updates based on Sponsor feedback to v2.3.<br>Updates to include additional TLFs for Part C.                                                                                                                                                                                                                                                            |
| v3.0 / 26JAN2024 | Minor clarification to description of PK Figures.<br>Version rounded for finalization prior to database lock.                                                                                                                                                                                                                                           |



3.0 Table of Contents

1.0 Approvals ..... 1

2.0 Change History ..... 2

3.0 Table of Contents ..... 3

4.0 Purpose ..... 5

5.0 Scope ..... 5

6.0 Introduction ..... 5

6.1 Changes from Protocol ..... 5

7.0 Study Objectives and Endpoints ..... 6

7.1 Primary Objectives ..... 6

Primary Endpoints ..... 6

7.2 Secondary Objectives ..... 7

Secondary Endpoints ..... 7

7.3 Exploratory Objectives ..... 8

Exploratory Endpoints ..... 9

8.0 Study Design ..... 9

8.1 Study Periods ..... 11

Screening Period ..... 11

Study Treatment Period ..... 11

End of Treatment (EoT) ..... 11

Follow-Up Period ..... 11

8.2 Sample Size Considerations ..... 12

8.3 Randomization ..... 12

9.0 Analysis Sets ..... 12

9.1 Enrolled Analysis Set ..... 12

9.2 All-Treated Analysis Set ..... 12

9.3 Dose Limiting Toxicity (DLT) Analysis Set ..... 12

9.4 Pharmacokinetic (PK) Analysis Sets ..... 13

PK Concentration Analysis Set ..... 13

PK Parameter Analysis Set ..... 13

PK Pre-Dose Concentration (C<sub>trough</sub>) Analysis Set ..... 13

9.5 Disease Response Analysis Set ..... 13

9.6 Clinically Evaluable Analysis Set ..... 13

10.0 Conventions and Derivations ..... 13

10.1 Baseline and Change from Baseline ..... 13

10.2 Durations ..... 14

10.3 Prior, Concomitant and Post Treatment Medications ..... 14

10.4 Efficacy ..... 14

Clinical Benefit Rate (CBR) ..... 15

Overall Response Rate (ORR) ..... 15

Disease Control Rate (DCR) ..... 16

Duration of Confirmed Response (DOR) ..... 16

Radiographic Progression-Free Survival (PFS) ..... 16

Overall Survival (OS) ..... 16

10.5 Study Drug Exposure ..... 17

Cycles Started ..... 17

Cumulative Dose Received ..... 17

Cumulative Planned Dose ..... 17

Dose Intensity ..... 17

10.6 Safety Variables ..... 17

Dose-Limiting Toxicity (DLT) ..... 17

Maximum Tolerated Dose (MTD) ..... 18

Recommended Phase 2 Dose (RP2D) ..... 18

Treatment Emergent Adverse Events (TEAEs) ..... 18

Treatment Related Adverse Events ..... 18

Laboratory Parameters ..... 18

Estimated Glomerular Filtration Rate (eGFR) ..... 20

Eastern Cooperative Oncology Group (ECOG) Performance Status ..... 20

Electrocardiogram Corrected QT Intervals ..... 20

10.7 Pharmacokinetic Variables ..... 20

Steady State ..... 20

10.8 Handling of Partial Dates ..... 20

11.0 Interim Analyses ..... 21

12.0 Statistical Methods ..... 21

12.1 Patient Disposition ..... 22

12.2 Demographic and Baseline Characteristics ..... 22

12.3 Treatments ..... 23

Extent of Study Drug Exposure ..... 23



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|                                                   |    |
|---------------------------------------------------|----|
| Concomitant Medications.....                      | 23 |
| 12.4 Important Protocol Deviations .....          | 23 |
| 12.5 Efficacy Analyses .....                      | 24 |
| Hypothesis Testing Strategy and Multiplicity..... | 24 |
| Primary Endpoint.....                             | 24 |
| Secondary Endpoints.....                          | 24 |
| 12.6 Exploratory Efficacy Analyses .....          | 25 |
| 12.7 Safety Analyses.....                         | 26 |
| Adverse Events .....                              | 27 |
| Deaths .....                                      | 27 |
| Laboratory Data.....                              | 27 |
| Vital Signs .....                                 | 28 |
| Other Observations Related to Safety.....         | 28 |
| Biomarkers .....                                  | 29 |
| 12.8 Pharmacokinetic Analyses.....                | 29 |
| Plasma Concentrations.....                        | 30 |
| Plasma Pharmacokinetic Parameters .....           | 31 |
| PK-PD Analysis .....                              | 36 |
| 13.0 References .....                             | 37 |
| 14.0 Appendix 1: Glossary of Abbreviations .....  | 37 |



## 4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Arvinas, Inc. ARV-471-mBC-101, Amendment 5.

## 5.0 Scope

The SAP outlines the following:

- Study Objectives and Endpoints
- Study Design
- Endpoints to be Analyzed and the Analysis Sets
- Applicable Study Definitions
- Statistical Methods

See Appendix 1 for a list of abbreviations used throughout this document. The list of the tables, listings and figures (TLFs) illustrating the analyses described in this SAP are presented in the accompanying TLF shells document.

Any deviation from the SAP will be described in the Clinical Study Report (CSR).

## 6.0 Introduction

This SAP describes the statistical methods to be used during the reporting and analyses of data collected under Arvinas, Inc. ARV-471-mBC-101, Amendment 5 dated 13MAR2023 and should be read in conjunction with version 10.0 of the case report form (CRF), dated 22MAY2023. Any changes to either the protocol or CRF may necessitate updates to the SAP.

Changes following approval of the first draft of the SAP will be tracked, the final version of the SAP will be issued for sponsor approval prior to database lock.

Throughout this document the Phase 1, Phase 2 and Phase 1b portions of the study will be referred to as Part A, Part B and Part C respectively, as indicated in the protocol.

### 6.1 Changes from Protocol

#### Analysis Sets

Section 9.3.1 of the Protocol specifies the definition of the Enrolled Analysis Set as "...successfully undergone the inclusion/exclusion assessment". This has been removed from the SAP definition after discussion with the sponsor, on the basis that completing the eligibility assessment should not imply passing eligibility criteria. This analysis set will be all patients consenting to participate, including screen failures. This is described in [Section 9.1](#) of the SAP.

Section 9.3.2 of the Protocol specifies the definition of the Safety Analysis Set. As some components of efficacy will use this analysis set, it was decided to rename this as the All-Treated Set, to avoid confusion when overlapping with efficacy.

Section 9.3.5 of the Protocol specifies the definition of the Efficacy Analysis Set and specifically its use in analyzing clinical benefit rate (CBR). As SD is considered a clinical benefit, and doesn't require measurable disease at baseline, to account for this a Clinically Evaluable Analysis Set is derived in [Section 9.6](#) of this SAP. As the Protocol specified Efficacy Analysis Set isn't used explicitly in the analysis of all efficacy components, it was decided to rename this as the Disease Response Set.

#### Pooling of Patients on Recommended Phase 2 Dose (RP2D)

Section 9.1 of the Protocol states that "*Patients from Part A who received the same dosing regimen as the RP2D will also be included in the analyses for Part B.*" During the SAP finalization, it was agreed that the efficacy analyses would keep each study part distinct and that the Part A patients receiving the RP2D will not be included in the Part B analysis.

#### Overall Response Rate (ORR)



Section 9.4.4.1 of the Protocol states that *“Patients with confirmed and unconfirmed responses will be included as responders”* in the context of overall response rate (ORR). During the SAP finalization, it was agreed that only confirmed responses would be included, though frequency counts of unconfirmed responses have been added to the ORR summary table.

### Overall Survival (OS)

In the Statistical Methods section of the protocol it specifies as part of the analysis of Overall Survival (OS) *“...a Kaplan-Meier plot of the time to censoring (including censoring of DLT), will be presented.”* During the SAP finalization, it was agreed to replace this with the arithmetic median follow-up time. This was added to the overall survival summary table.

### Concomitant Medications

Section 6.4 of the Protocol defines a concomitant therapy as *“Any medication... 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..”* During the SAP finalization, it was agreed to amend this to medications received in combination with study treatment, up to 30 days after the last dose, this is described in [Section 10.3](#) of this SAP.

### Treatment Compliance

Section 6.3 of the Protocol explains that compliance is based on the drug accountability information, with sites recording dispensed and returned tablet information. However as information regarding tablet strength is not recorded, hence the planned number of tablets to be taken for a given patient is unknown. The decision was made to remove compliance and use absolute and relative dose intensities as an alternative summary measure. These are described in [Section 10.5](#) of this SAP.

### General Presentation of Tables

Where the protocol refers to the presentation by Cohort (as an example, in Section 9.4.1; *“The study disposition of every enrolled patient will be presented by cohorts.”*) this has been replaced by Total Daily Dose given at Cycle 1 Day 1. In other words, where different cohorts have the same total daily dose, those patients are pooled into the same column within a summary table.

## 7.0 Study Objectives and Endpoints

### 7.1 Primary Objectives

#### Part A

- To evaluate safety and tolerability of ARV-471 in successive cohorts of patients in order to estimate the maximum tolerated dose (MTD) and select the recommended phase 2 doses (RP2Ds).

#### Part B

- To evaluate the anti-tumor activity of ARV-471 in patients with locally advanced or metastatic breast cancer (mBC).

#### Part C

- To evaluate the safety and tolerability of ARV-471 in combination with Palbociclib and select the recommended dose/schedule for the combination.

## Primary Endpoints

### Part A



- First Cycle DLTs.
- AEs as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria Adverse Event [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.

**Part B**

- The anti-tumor activity of ARV-471 will be assessed by evaluating CBR based on the summation of CRs, PRs and SD of 24 weeks duration or longer.

**Part C**

- As per Part A, plus;
- Determination of an MTD, if applicable, among the doses evaluated.

## 7.2 Secondary Objectives

**Part A**

- To characterize the single dose and steady-state pharmacokinetic (PK) of ARV-471 and ARV-473 (an epimer of ARV-471).
- To explore preliminary anti-tumor activity.

**Part B**

- To further evaluate the anti-tumor activity of ARV-471 in patients with locally advanced or mBC.
- To further evaluate the safety and tolerability of ARV-471 in patients with locally advanced or mBC.
- To determine plasma concentrations of ARV-471 and ARV-473.

**Part C**

- To characterize the first dose and steady state PK of ARV-471 and ARV-473 (an epimer of ARV-471) and Palbociclib when ARV-471 is administered in combination with palbociclib.
- To characterize the steady state PK of Palbociclib when given alone and in combination with ARV-471 in Cohort C5.
- To assess preliminary anti-tumor activity of ARV-471 in combination with Palbociclib.

## Secondary Endpoints

**Part A**

- The following PK parameters will be assessed when applicable after a single dose and after multiple doses:
  - $AUC_{0-\tau}$ ,  $AUC_{0-last}$ ,  $C_{max}$ ,  $C_{min}$ ,  $CL/F$ ,  $T_{max}$ ,  $Vd/F$ , accumulation ratios, Effective  $T_{1/2}$ ,  $MRC_{max}$ , and  $MRAUC_{0-\tau}$ . (Refer to Protocol Table 18 for definitions)
- Anti-tumor activity of ARV-471 will be assessed by evaluating the following:
  - ORR per Response evaluation criteria in solid tumors (RECIST) 1.1 in patients with measurable disease at baseline
  - CBR based on the summation of CRs, PRs and 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 B

- 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
  - Time to event endpoints:
    - PFS
    - DOR
    - OS
- AEs as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria Adverse Event [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.
- Pre-dose concentrations of ARV-471 and ARV-473.

## Part C

- The following PK parameters will be assessed for ARV-471, ARV-473 and Palbociclib when applicable after a single dose and after multiple doses:
  - $AUC_{0-\tau}$ ,  $AUC_{0-last}$ ,  $C_{max}$ ,  $C_{min}$ ,  $CL/F$ ,  $T_{max}$ ,  $Vd/F$ , accumulation ratios, Effective  $T_{1/2}$ ,  $MRC_{max}$ , and  $MRAUC_{0-\tau}$ . (Refer to Protocol Table 18 for definitions)
- PK parameters of Palbociclib  $AUC_{0-\tau}$ , and  $C_{max}$ , and other PK parameters if data permits ( $T_{max}$ ,  $CL/F$ ,  $Vd/F$ , etc)
- 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 SD of 24 weeks duration or longer
  - Time to event endpoints:
    - PFS
    - DOR
    - OS

## 7.3 Exploratory Objectives

### Part A

- To characterize baseline estrogen receptor 1 (ESR1) mutational status, which is a potential mechanism of resistance to prior estrogen receptor (ER)-targeted therapies, and relevant molecularly defined subsets of patients.
- To assess pharmacodynamic effects of ARV-471 on exploratory biomarkers.

### Part B



- 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
- To assess pharmacodynamic biomarkers of ARV-471

Part C

- To characterize tumor mutational status, including ESR1, which is a potential mechanism of resistance to prior ER-targeted therapies.
- To assess pharmacodynamic effects of ARV-471 on exploratory biomarkers.

Exploratory Endpoints

Part A, Part B and Part C

- ESR1 mutational status in Circulating tumor deoxyribonucleic acid (ctDNA) and/or tumor tissue.
- ER, progesterone receptor, and Ki-67 protein levels in pre and post-treatment tumor biopsies in patients with accessible tumor tissue.

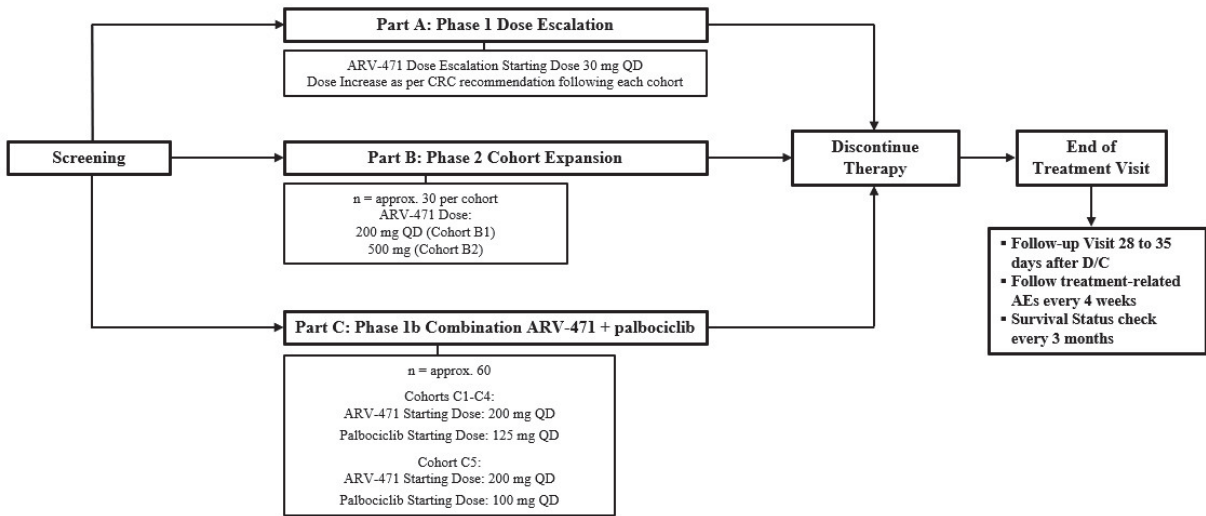
8.0 Study Design

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 MTD and/or 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.

Figure 1 Overall Study Schema



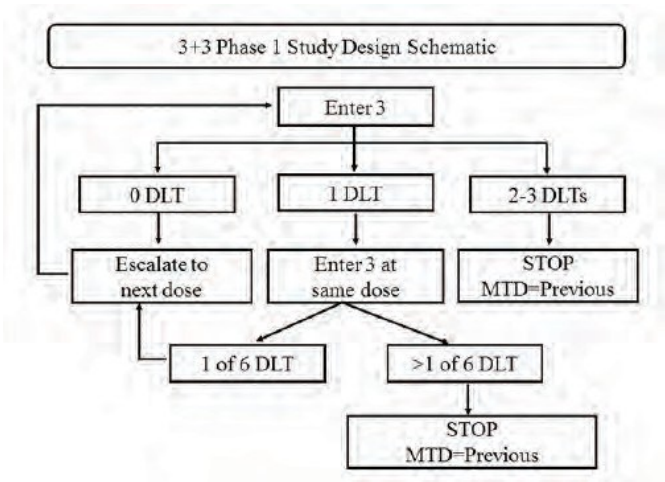
Abbreviations: AE=Adverse Event; CRC=Cohort Review Committee; D/C=Discontinuation; QD=Once Daily.

Part A (Phase 1 Dose Escalation)



Part A 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 (See [Figure 2](#)). The first cohort will be Cohort 1 and subsequent cohorts will be Cohort 2, Cohort 3, etc.

**Figure 2      3+3 Study Design Schema**



Additional patients (up to 20 total per dose) may be added to a previously studied dose escalation cohort once the Cohort Review Committee (CRC) has deemed the dose to be safe. These additional patients are required to have accessible lesions for biopsy and must agree to mandatory pre and post-treatment core biopsies which will allow for further characterization of the safety of ARV-471 as well as its PK/pharmacodynamic 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.

Patients will be monitored for treatment-emergent adverse events (TEAEs) and dose-limiting toxicities (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 (PD), unacceptable toxicity, or withdrawal of consent.

**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 Cyclin-Dependent Kinase (CDK) 4/6 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 (Phase 1b Combination)**

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).

Part C will include 2 dose-escalation levels for ARV-471 in combination with Palbociclib prior to the expansion cohort:

- 1. 200 mg QD (Cohort C1; initially 180 mg QD, rounded up to 200 mg QD upon availability of the 100-mg tablets),
- 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, based on the determined RP2D from the monotherapy portion of the trial. 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 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. 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 Safety Review Committee (SRC) will then continue to monitor safety throughout Part C for the patients receiving the recommended dose of ARV-471 in combination with Palbociclib.

## 8.1 Study Periods

All parts 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 Protocol Section 7.1). Patients who have evidence of radiographic PD may be considered for continued study therapy provided the Principal Investigator has determined that they are still benefiting from study therapy.

### End of Treatment (EoT)

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 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 on the AE electronic CRF (eCRF) page.

### Follow-Up Period

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.



## 8.2 Sample Size Considerations

### Part A

It is anticipated that 4-8 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 will be enrolled in Part A 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 approximately 60 patients for the Clinically Evaluable Analysis Set will provide estimation of the CBR with 95% confidence interval (CI) width 24.4% (or 34.7% for each cohort), if the observed CBR is 30% (i.e. the 95% CI based on the Clopper-Pearson method for the CBR will be estimated as 18.8%, 43.2%).

The sample size of 60 patients in the Efficacy Analysis Set will provide estimation of the ORR to have a 95% CI width of 16.8%, if the ORR is 10%, i.e., the 95% CI for the response rate will be estimated as (3.8%, 20.5%).

### Part C

Approximately 6-12 evaluable patients will be enrolled in a dose escalation in combination with Palbociclib, followed by approximately 40 evaluable patients (approximately 20 in each 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. Therefore, approximately 60 patients will be enrolled into Part C of this study, when the full cohort of patients is included.

## 8.3 Randomization

Randomization will not be performed on this study. If both cohorts in Part B are open to accrual simultaneously, sequential patients may be enrolled to each cohort in an alternating fashion.

## 9.0 Analysis Sets

### 9.1 Enrolled Analysis Set

The Enrolled Analysis Set consists of patients who are registered to participate in this study with informed consent signed.

### 9.2 All-Treated Analysis Set

The All-Treated Analysis Set consists of all enrolled patients who have received any amount of ARV-471 dose (partial or complete) for monotherapy cohorts or any study drug for combination therapy cohorts. For details on the label change from the Safety Analysis Set, refer to [Section 6.1](#).

The All-Treated 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.

Some efficacy parameters such as PFS and OS will be evaluated using the All-Treated Analysis Set.

### 9.3 Dose Limiting Toxicity (DLT) Analysis Set

The DLT Analysis Set is defined for Part A and Part C patients.

- For Part A, the DLT Analysis Set includes all patients 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. Backfill patients (identified via the Enrollment eCRF page), are excluded from the DLT Analysis Set.



- 
- For Part C the DLT Analysis Set includes patients from Cohorts C1 and C2 only, 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.

## 9.4 Pharmacokinetic (PK) Analysis Sets

### PK Concentration Analysis Set

The PK Concentration Analysis Set includes all patients in the All-Treated Analysis Set who have at least one plasma concentration (including those below the limit of quantification [BLOQ]) for ARV-471, ARV-473 or Palbociclib.

### PK Parameter Analysis Set

The PK Parameter Analysis Set will include all patients in the All-Treated Analysis Set who have at least one PK parameter of interest for ARV-471, 473, or Palbociclib ( $C_{max}$  or AUC).

### PK Pre-Dose Concentration ( $C_{trough}$ ) Analysis Set

The PK Pre-Dose Concentration Analysis Set will include all patients in All-Treated Analysis Set who have at least one evaluable  $C_{trough}$  and within the allowable time window following treatment for ARV-471, ARV-473 or Palbociclib.

The allowable time window for the PK Pre-Dose sample is defined in the following way;

- Dosing time from the day prior to PK sample collection is known;  
The allowable time window is the period of time between 22 hours after dosing on the day prior to the sample collection, and the time of dosing on the day of sample collection.
- Dosing time from the day prior is not available;  
The allowable time window is the period of time between 2 hours before dosing and the time of dosing on the day of sample collection.

## 9.5 Disease Response Analysis Set

The Disease Response Analysis Set will be comprised of all patients in the All-Treated Analysis Set with baseline and at least 1 post-baseline radiographic assessment (computed tomography [CT] or magnetic resonance imaging [MRI] scan). For details on the label change from the Efficacy Analysis Set, refer to [Section 6.1](#).

The Disease Response Analysis Set will be used for the summary of efficacy endpoints such as ORR and DOR. The ORR analysis will be limited to patients with measurable disease by RECIST 1.1. DOR analysis will be limited to responders.

## 9.6 Clinically Evaluable Analysis Set

The Clinically Evaluable Analysis Set will be comprised of all patients in the All-Treated analysis set and are either a Responder (best overall response of CR/PR) or a Non-Responder with a potential treatment duration of at least 24 weeks prior to any data cutoff.

The Clinically Evaluable Analysis Set will be used specifically for the summary of CBR.

## 10.0 Conventions and Derivations

### 10.1 Baseline and Change from Baseline

Baseline is defined as the last available observation prior to the first administration of ARV-471 on Cycle 1 Day 1 for monotherapy cohorts or prior to the first administration of any study drug for combination therapy cohorts.



Change from baseline will be defined as the post-baseline value minus the baseline value, where applicable (on a patient level). Change from baseline will only be calculated for patients who have both baseline and at least one post-baseline value for a given parameter.

Percentage change from baseline = 100 x (Change from Baseline / Baseline Value)

10.2 Durations

- Time Since [Event] (months) = (Informed Consent Date - Event Date) / 30.4375  
where the Event is either Diagnosis or Locally Recurrent Disease
- Duration of Exposure (weeks) = [(Last Dose Date - First Dose Date) + 1] / 7

For the details on the efficacy parameters of DOR, PFS and OS, refer to [Section 10.4](#).

10.3 Prior, Concomitant and Post Treatment Medications

Prior medications are defined as any medication with a start date and end date prior to the day of first dose of study medication.

Concomitant medications are defined as any non-study medication or vaccine (including over-the-counter or prescription medicines, vitamins, physiologic replacement doses of systemically administered corticosteroids and/or herbal supplements) that the patient receives on or after the day of first dose of study medication, up to and including 30 days after the last dose of study medication.

Post Treatment medications are medications that started beyond 30 days of last dose of study medication.

10.4 Efficacy

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 version 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 CR, PR, SD, PD and not evaluable (NE).

Confirmed responses (CR, PR), are those performed at least 4 weeks after the criteria for response were first met. These confirmed responses will be used in the derivations for CBR, ORR, DCR, and DOR. Refer to [Table 1](#) for the algorithm defining confirmed response.

**Table 1** Confirmed Response based on Subsequent Assessments\*

| First Time Point Response** | Second Time Point Response | Confirmed Response (Best Response)* |
|-----------------------------|----------------------------|-------------------------------------|
| PD                          | No further evaluation      | PD                                  |
| NE                          | PD                         | PD                                  |
| CR                          | PD                         | SD or PD (1)                        |
| PR                          | PD                         | SD or PD (1)                        |
| SD                          | PD                         | SD or PD (1)                        |
| CR                          | CR                         | CR                                  |
| CR                          | NE **                      | SD or NE (2)                        |
| PR                          | CR                         | PR                                  |
| PR                          | PR                         | PR                                  |



| First Time Point Response** | Second Time Point Response | Confirmed Response (Best Response)* |
|-----------------------------|----------------------------|-------------------------------------|
| PR                          | SD (3)**                   | SD                                  |
| PR                          | NE **                      | SD or NE (2)                        |
| SD                          | CR                         | SD                                  |
| SD                          | PR                         | SD                                  |
| SD                          | SD                         | SD                                  |
| SD                          | NE                         | SD or NE (2)                        |
| NE                          | CR                         | SD                                  |
| NE                          | PR                         | SD                                  |
| NE                          | SD                         | SD                                  |
| NE                          | NE                         | NE                                  |

\* A Best Response of SD can only be made after the patient is on-study for a minimum of 51 days (8 weeks [56 days] allowing for the protocol defined 5 day assessment window). If the patient is on-study less than 51 days, any tumor assessment indicating SD before this time period will have a Best Response of NE unless PD is identified.

\*\* Subsequent documentation of CR may provide confirmation of a previously identified CR for patients where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for patients where the second integrated response was NE or SD. If the third time point response confirms the CR (or PR) then the confirmed response will be CR (or PR). For this study, only one intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one SD is allowed between PRs (e.g., PR SD PR = PR).

- (1) Best response will be SD if the first time point response is after at least 51 days on-treatment. Otherwise, the best response will be PD.
- (2) Best response will be SD if the first time point response is after 51 days on-study. Otherwise, the best response will be NE.
- (3) Time point response is SD if the increase from the first to the second assessment does not qualify for PD.

For patients with unconfirmed CR/PR and who subsequently discontinue study participation early, the best overall response will be SD.

### Clinical Benefit Rate (CBR)

The primary efficacy variable is the CBR<sub>24</sub>, based on the summation of CRs, PRs and SD. SD must be of 23.28 weeks duration or longer to be included. The number of patients in the Clinically Evaluable Analysis Set will be used as the denominator.

Note that 23.28 weeks is used in place of the protocol defined 24 weeks, to account for the protocol permitted 5-day window around the assessment visits. This modification allows for a SD assessed 5 days prior to the 24 week time point to be included in the CBR<sub>24</sub> analyses.

### Overall Response Rate (ORR)

ORR is defined as the percentage of patients with a best overall response of CR or PR, where best response is determined from all visit responses prior to receiving alternative cancer treatment, using the following sequential order: CR, PR, SD, PD, and NE. The number of patients in the Disease Response Analysis Set with measurable disease will be used as the denominator.



### Disease Control Rate (DCR)

DCR is defined as the percentage of patients with a confirmed best overall response of CR, PR or SD. The number of patients in the Disease Response Analysis Set will be used as the denominator.

### Duration of Confirmed Response (DOR)

DOR is defined as 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. The number of patients in the Disease Response Analysis Set with measurable disease who had a best overall confirmed response of CR or PR, will be used.

Any patient who does not have documented PD will be censored on the date of their last evaluable assessment, as per the following guidelines:

- Patients on-study and progression-free at data cutoff or End of Study;
- Patients who are lost to follow-up or withdraw consent;
- Patients given alternative cancer treatment prior to PD or death on-study;
- Patients who have PD or death on study after  $\geq 2$  consecutive missed tumor assessments (i.e., >16 weeks + 10 days after the last on-study disease assessment).

The DOR is calculated as:

- $\text{DOR (months)} = (\text{Date of PD or Death} - \text{Date of First Documented CR/PR} + 1) / 30.4375 \text{ (months)}.$

### Radiographic Progression-Free Survival (PFS)

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. As it is possible that patients could be censored, or die before a post baseline assessment, the All-Treated Analysis Set will be used for analysis of PFS.

The PFS time is calculated as:

- $\text{PFS time (months)} = (\text{Date of PD or Death} - \text{Date of First Study Dose} + 1) / 30.4375 \text{ (months)}.$

PFS data will be censored for the patients who do not have documented PD or death. The following censoring rules that will be used:

- Event time will be censored on the date of the first dose with duration of 1 day for;
  - Patients lacking any evaluation of disease after first study treatment (unless, they die within 2 tumor assessments of baseline, this will be treated as an event with the date of death as the event date).
- Event time will be censored on the date of the last evaluable assessment documenting absence of PD for:
  - Patients on-study and progression-free at data cutoff or End of Study;
  - Patients who are lost to follow-up or withdraw consent;
  - Patients given alternative cancer treatment prior to PD or death on-study;
  - Patients who have PD or death on study after  $\geq 2$  consecutive missed tumor assessments (i.e., >16 weeks + 10 days after the last on-study disease assessment).

### Overall Survival (OS)

Overall survival is the time interval from the date of first study dose to the date of death due to any cause. Any patient without a reported date of death will be censored on the date the patient was last known to be alive. The All-Treated Analysis Set will be used for analysis of OS.



## 10.5 Study Drug Exposure

### Cycles Started

A patient is considered to have started a cycle if they received at least one dose in that cycle, per the Dose Administration eCRF page or the dosing log.

### Cumulative Dose Received

Cumulative dose received (mg) is defined as the total amount of the study drug a patient receives during the study. That is, the sum of doses administered across the study treatment period as recorded on the Dose Administration and Dosing Diary eCRF pages.

This is calculated by taking the dose from the first entry on the Dose Administration eCRF page and assigning it to all entries of the Dosing Diary eCRF pages where it indicates a dose was taken as prescribed. If a subsequent Dose Administration eCRF page indicates a different dose was given, this new dose will be assigned moving forward. In the event the dosing diary has missing records, or that the collected data indicates no dose was administered, then these instances will be treated as 0mg being received. Dose adjustments as recorded on Dose Administration eCRF page will be accounted for in the cumulative dose received calculations.

### Cumulative Planned Dose

Planned dose for ARV-471 is calculated as the starting daily dose multiplied by the number of days between the actual date of first dose and the actual date of last dose, (i.e., duration of exposure).

Planned dose for Palbociclib (planned 3-weeks on, 1-week off-treatment schedule) is calculated as;

- Starting daily dose multiplied by  $([x/28]*21) + \text{Minimum of } (x-[x/28]*28 \text{ or } 21)$

Where  $[x/28]$  is the integer part of  $x/28$ , and  $x$  is the number of days between the actual date of first dose and the actual date of last dose, (i.e. duration of exposure).

For example (Duration of Exposure is 78 days,  $x=78$ )

- $[x/28] = 2$  (Integer of 2.786)
- $(2*21) + \text{Min}([78-(2*28)] \text{ or } 21)$
- $42 + 21 = 63$  Days Exposure to Palbociclib.

### Dose Intensity

Absolute Dose Intensity is calculated as;

- Cumulative Dose Received (mg) / Duration of Exposure (weeks).

Relative Dose Intensity is calculated as;

- Cumulative Dose Received (mg) / Planned Cumulative Dose (mg),

## 10.6 Safety Variables

### Dose-Limiting Toxicity (DLT)

DLTs will be evaluated during the first cycle and identified on the AEs eCRF page. Refer to Appendix 5 of the Protocol for the definition of a DLT.



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**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 cohort 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 (RP2D)**

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.

**Treatment Emergent Adverse Events (TEAEs)**

A TEAE is an AE occurring on/after the date of first study dose and within 30 days of the last study dose.

**Treatment Related Adverse Events**

The relationship of AEs to study drug will be dichotomized as "Related" or "Unrelated". AEs assessed by the Principal Investigator to be "Not Related" or "Unlikely Related" will be categorized as "Unrelated" and AEs assessed to be "Possibly Related", "Probably Related" or "Related" will be categorized as "Related". Any AEs with a missing relationship, will be conservatively categorized as "Related".

**Laboratory Parameters**

Clinical laboratory parameters to be collected routinely for hematology, chemistry, coagulation and urinalysis. Other laboratory parameters are collected for viral serology, thyroid profile, pregnancy and tumor markers. All parameters are listed in [Table 2](#).



Table 2 Laboratory Parameters

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <div><b>Hematology Panel</b><ul style="list-style-type: none"><li>• Platelet Count <sup>Low</sup></li><li>• Red Blood Cell Count</li><li>• Hemoglobin <sup>Low</sup></li><li>• Hematocrit</li><li>• White Blood Cell Count with Differential;<ul style="list-style-type: none"><li>○ Absolute Neutrophils <sup>Low</sup></li><li>○ Absolute Lymphocytes <sup>Low</sup></li><li>○ Absolute Monocytes</li><li>○ Absolute Eosinophils</li><li>○ Absolute Basophils</li><li>○ White Blood Cells <sup>Low</sup></li></ul></li></ul></div> | <div><b>Chemistry Panel</b><ul style="list-style-type: none"><li>• Blood Urea Nitrogen (BUN)</li><li>• BUN or Urea</li><li>• Glucose (non-fasting)</li><li>• Creatinine <sup>High</sup></li><li>• Creatine Kinase</li><li>• Creatine Kinase MB Fraction*</li><li>• Magnesium</li><li>• Potassium <sup>High or Low</sup></li><li>• Sodium <sup>High or Low</sup></li><li>• Total Calcium <sup>High or Low</sup></li><li>• Lactate Dehydrogenase (LDH) <sup>Grade 1</sup></li><li>• Albumin <sup>Low</sup></li><li>• Uric acid</li><li>• Carbon Dioxide (Bicarbonate)</li><li>• Aspartate Aminotransferase (AST) <sup>High</sup></li><li>• Alanine Aminotransferase (ALT) <sup>High</sup></li><li>• Alkaline Phosphatase (ALP) <sup>High</sup></li><li>• Chloride</li><li>• Amylase</li><li>• Total Bilirubin <sup>High</sup></li><li>• Direct, Conjugated and Unconjugated Bilirubin*</li><li>• Total Protein</li><li>• Phosphorus or Phosphate</li></ul></div> |
| <div><b>Coagulation</b><ul style="list-style-type: none"><li>• International Normalized Ratio (INR)</li><li>• Prothrombin Time</li><li>• Partial Prothrombin Time</li><li>• Activated Partial Thromboplastin Time (aPTT)</li></ul></div>                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <div><b>Urinalysis</b><ul style="list-style-type: none"><li>• Leucocyte Esterase</li><li>• Protein</li><li>• Urine Bilirubin</li><li>• Urobilinogen</li><li>• Ketones</li><li>• Microscopy*</li><li>• pH</li><li>• Nitrites</li><li>• Specific Gravity</li><li>• Glucose (qual)</li><li>• Blood (qual)</li></ul></div>                                                                                                                                                                                                               | <div><b>Other</b><ul style="list-style-type: none"><li>• Viral Serology<ul style="list-style-type: none"><li>○ HIV I and II</li><li>○ Hepatitis C Virus</li><li>○ HBsAg</li></ul></li><li>• Thyroid Profile<ul style="list-style-type: none"><li>○ Thyroid Stimulating Hormone (TSH)</li></ul></li><li>• Pregnancy<ul style="list-style-type: none"><li>○ Serum at Screening</li><li>○ Urine on Study</li></ul></li><li>• Tumor Markers (CA 15-3, CA 27.29, CEA)</li></ul></div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

Low: Indicates parameter where most severe values are low.  
High: Indicates parameter where most severe values are high.  
High or Low: Indicates parameter where most severe values can be in either direction.  
Grade 1: Indicates parameter is graded as either Grade 0 or Grade 1.  
\*: Indicates parameter will be performed if clinically indicated.



Estimated Glomerular Filtration Rate (eGFR)

Estimated glomerular filtration rate (eGFR) will be derived in the laboratory analysis dataset, using the Chronic Kidney Disease Epidemiology (CKD-EPI) Creatinine Equation (2021). The formula is specified here;

- eGFR (mL/min/ 1.73 m2) = 142 \* min(Scr/K, 1)<sup>α</sup> \* max(Scr/K, 1)<sup>-1.200</sup> \* 0.9938Age \* 1.012 [if female],  
where; Scr (Serum Creatinine) in mg/dL  
K = 0.7 (Females) or 0.9 (Males)  
α = -0.241 (Females) or -0.302 (Males)  
min = the minimum of Scr/K or 1  
max = the maximum of Scr/K or 1

Eastern Cooperative Oncology Group (ECOG) Performance Status

Table 3 ECOG Performance Status

| ECOG | ECOG Performance Status                                                                                                                                   |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0    | Fully active, able to carry on all pre-disease performance without restrictions                                                                           |
| 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 walking hours                           |
| 3    | Capable of only limited selfcare; confined to bed or chair more than 50% of walking hour                                                                  |
| 4    | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair                                                                       |
| 5    | Dead                                                                                                                                                      |

Electrocardiogram Corrected QT Intervals

The corrected QT interval by Bazett’s method (QTcB) and the corrected QT interval by Fredericia’s method (QTcF) are collected on the CRF. If duplicate/triplicates of QTcB/QTcF are available at a given time point, the average will be derived.

10.7 Pharmacokinetic Variables

Steady State

ARV-471 concentration is considered steady-state when a patient has received at least 7 consecutive days of ARV-471 (any dose).  
Palbociclib concentration is considered steady-state when a patient has received at least 7 consecutive days of palbociclib (any dose).

10.8 Handling of Partial Dates

No imputation for missing or partial dates prior to enrollment will be performed (e.g. Diagnosis Date). Any durations based on these dates will therefore also be missing.  
The following rules will be applied to impute missing start and end dates in appropriate data types (e.g., AEs or concomitant medications).

Start Date



If the start date is completely missing (i.e., the day, month, and year are all unknown) the start date will be set to the date of first dose of study medication.

#### Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the **first dose date**, then the day of the **first dose date** will be assigned to the missing day of **start date**.
- If either the year is before the year of the **first dose date** or if both years are the same but the month is before the month of the **first dose date**, then the last day of the month will be assigned to the missing day of **start date**.
- If either the year is after the year of the **first dose date** or if both years are the same but the month is after the month of the **first dose date**, then the first day of the month will be assigned to the missing day.

#### Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the below procedure.

#### Missing Day and Month

- If the year of the incomplete date is the same as the year of the **first dose date**, then the day and month of the **first dose date** will be assigned to the missing fields.
- If the year of the incomplete date is not the same as the year of the first dose date, then January 1 will be assigned to the missing fields.

If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

#### End Date

##### Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the last visit date, then the day of the last visit date will be assigned to the missing day.
- If either the year is before the year of the last visit date or if both years are the same but the month is before the month of the last visit date, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last visit date or if both years are the same but the month is after the month of the last visit date, then the first day of the month will be assigned to the missing day.

##### Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the below procedure.

##### Missing Day and Month

- If the year of the incomplete date is the same as the year of the **last visit date**, then the day and month of the **last visit date** will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the **last visit date**, then December 31 will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the **last visit date**, then December 31 will be assigned to the missing fields.

## 11.0 Interim Analyses

No formal interim analyses are planned for this study.

## 12.0 Statistical Methods

All data collected during this study will be displayed in patient data listings, unless otherwise specified. Data listings will be sorted by study part, cohort, dose (at Cycle 1 Day 1) and patient identifier. Screen failures will be excluded from all tables and listings, with the exception being the listing of screen failures.



Continuous (quantitative) variables will be summarized using univariate statistics (number of non-missing values [n], mean, median, standard deviations [STD], minimum and maximum values). Where appropriate, estimates will be presented with 95% CIs. Mean and median will be presented to 1 decimal more than original data. STD will be presented to 2 decimals more than original data. Minimum and maximum will match the decimal points in the original data.

Categorical (qualitative) variables will be summarized descriptively by frequency tables showing the number and percentage of patients within a category. In general, the denominator for the percentage calculation will be based upon the total number of patients in the study population for the treatment group. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal place and percentages will not be displayed for zero counts. Time-to-event data will be presented using KM and Swimmer plots.

For Safety and Efficacy, analyses will be presented by study part, Cycle 1 Day 1 total daily dose and overall, unless otherwise specified in the sections below. For PK, analyses will be presented by study part and Cycle 1 Day 1 initial dose group (defined as the initial C1D1 dose/frequency received prior to PK samples being obtained).

The statistical analysis will be performed using SAS 9.4 or higher. The final TLFs as well as the clinical study report (CSR) will be prepared after the database is locked.

Unless otherwise noted, the statistical analyses described below are applicable to Part A, Part B and Part C.

## 12.1 Patient Disposition

The disposition of patients in the Enrolled Analysis Set will be summarized descriptively for;

- Patients within each analysis set.
- Patients enrolled by site.
- Patients who are still on-treatment, who completed/discontinued treatment and who completed/discontinued study, along with the reasons for completion/discontinuation.

All enrolled patients will be presented in a listing along with indication of study completion, date of completion/discontinuation, primary reason for discontinuation and date of first study dose and last study dose.

The patients who discontinue treatment early will also be presented in a listing along with the reason for discontinuation, date of treatment discontinuation and indication of continuation through follow-up visits. A separate listing of screen failures will also be produced.

## 12.2 Demographic and Baseline Characteristics

The demographic, baseline characteristics and medical history (including disease history) will be presented for patients in the All-Treated Analysis Set.

The demographic and baseline variables, including age (years), height (cm), weight (kg), body mass index (BMI) ( $\text{kg}/\text{m}^2$ ), ECOG performance, ESR1 mutation status, and Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) distribution will be summarized descriptively. The categorical variables for sex (and childbearing potential for females), ethnicity, race and age group ( $< 65$ ,  $\geq 65$  years) will be presented by frequency and percentage.

Breast cancer history will be summarized descriptively for initial diagnosis (ER+, HER2-, ER+ and HER2-), recurrence (local and metastatic), stage of initial diagnosis and the time since diagnosis.

The extent of disease at baseline will be summarized descriptively for the number of metastatic sites (both as continuous and categorical), the number of patients with visceral metastasis (the presence of at least one Bile Duct, Bronchus, Liver, Lung, Peritoneum, Pleura or Pleural Cavity site at baseline) and measurable disease at baseline.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or higher, and summarized by SOC and PT.

Listings will be presented for demographic and baseline characteristics, medical history and breast cancer history separately.



## 12.3 Treatments

### Extent of Study Drug Exposure

Exposure will be summarized for patients in the All-Treated Analysis Set by study part, Cycle 1 Day 1 total daily dose, overall and additionally for Part C, by study drug. Descriptive statistics will be provided for the duration of exposure (weeks), the total number of cycles started, number of doses received, cumulative dose received (mg) absolute and relative dose intensities as well as compliance. The number and percentage of patients with compliance  $\geq 80\%$  -  $\leq 120\%$  will be presented. Patients with at least one dose adjustment along with the associated reasons for dose adjustment will also be presented.

Dose administration, drug accountability and treatment compliance will also be listed.

### Concomitant Medications

All medications received will be coded using World Health Organization Drug Dictionary (WHODD) (Version March 2019 [Global B3] or higher).

Both prior and concomitant medications will be summarized separately for patients in the All-Treated Analysis Set and will be presented by anatomical therapeutic chemical (ATC) classification level 2 and preferred drug name.

A listing will be presented for all, including post-treatment, medications along with indication as to whether each record was prior, concomitant or post treatment.

A summary of prior anti-cancer therapies will be presented for all settings (therapy setting, type of therapy and best response to most recent regimen), all settings excluding preventative (number of prior regimens and prior hormonal regimens, duration of the most recent prior hormonal regimen and selected prior medications of interest) and the metastatic setting (number of prior regimens and prior chemotherapy regimens).

The selected prior medications of interest are grouped as below, with each of the respective WHODD preferred drug names listed;

- Selective Estrogen Receptor Modulators (SERM)
  - Tamoxifen, Toremifene, Raloxifene
- Selective Estrogen Receptor Degradors (SERD) / ERs
  - Fulvestrant
- Aromatase Inhibitors (AI)
  - Letrozole, Exemestane, Anastrozole
- CDK4/6i
  - Abemaciclib, Palbociclib, Ribociclib

A listing will also be provided for both prior and follow-up systemic anti-cancer therapies.

## 12.4 Important Protocol Deviations

Protocol deviations data will be entered into a Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the deviation data from CTMS.

Deviations will be categorized as: inclusion/exclusion criteria not met, study drug deviation, prohibited medication received, overdose/misuse, study procedures not performed, out of visit window, etc. The study team will also categorize protocol deviations as important or not important. Final review of protocol deviations will be conducted and finalized prior to locking the database.

The number of patients with at least one important protocol deviation and the number of patients with at least one non-important protocol deviation within each deviation category will be presented based on the All-Treated Analysis Set. Important and non-important protocol deviations are defined per the study Protocol Deviation Guidance document. All protocol deviations will be listed.

A listing of patients who enroll with inclusion or exclusion criteria exceptions will also be provided.



## 12.5 Efficacy Analyses

The Disease Response and the Clinically Evaluable Analysis Sets will be used for analysis of the RECIST v1.1 tumor assessment endpoints (ORR, CBR, DCR and DOR). The All-Treated Analysis Set will be used for the analysis of PFS and OS.

### Hypothesis Testing Strategy and Multiplicity

Formal hypothesis testing or inferential statistical analysis comparing efficacy data among ARV-471 dose cohorts or historical data is not planned and hence no adjustments for multiple comparisons are required.

### Primary Endpoint

A primary efficacy endpoint is only defined for Part B, which is the CBR<sub>24</sub> (defined in [Section 10.4](#)). Analysis will be based on the Clinically Evaluable Analysis Set, presented by Cycle 1 Day 1 total daily dose. The count and proportion of patients achieving clinical benefit will be summarized along with two-sided exact (Clopper-Pearson) 95% binomial CIs for the proportion. CBR data will also be presented in a listing.

No primary efficacy endpoints are defined for Part A or Part C, refer to [Section 7.2](#) for secondary efficacy endpoints.

### Secondary Endpoints

The secondary endpoints for each study part are described in [Section 7.2](#) and defined in [Section 10.4](#). Secondary endpoints will be analyzed as described in following sections.

#### 12.5.1.1 Overall Response Rate (ORR)

The number of patients in the Disease Response Analysis Set with measurable disease will be used as the denominator for ORR. Part B and Part C will be presented by Cycle 1 Day 1 total daily dose, whilst Part A is presented as an overall group only. The count and percentage of overall response will be presented along with two-sided exact 95% CI for the percentage, estimated using the Clopper-Pearson methodology. Counts and percentages of patients with a best response of CR, PR, SD, PD or NE will also be presented.

The maximum percentage change from baseline in total tumor size (the sum of target lesions), defined as the maximum decrease or minimum increase for each patient, will be presented in a waterfall plot.

Swimmer plots will also be provided at the patient level, displaying the duration of treatment overlaid with the BOR for patients in the Disease Response Analysis Set.

Lesions assessed by the investigator (target, non-target, and new lesions) as well as both investigator-reported and derived RECIST v1.1 disease assessments will be presented in listings.

#### 12.5.1.2 Clinical Benefit Rate (CBR)

The secondary endpoint of CBR<sub>24</sub> for Part A and Part C will follow the same methods described in [Section 10.4](#) for Part B.

#### 12.5.1.3 Disease Control Rate (DCR)

The secondary endpoint of DCR is specified in the Protocol for Part A only, however Part B and Part C are included as exploratory efficacy analyses described in [Section 12.6](#).

The number of patients in the Disease Response Analysis Set will be used as the denominator for DCR. The number of patients achieving disease control will be presented by Cycle 1 Day 1 total daily dose. The two-sided 95% CI will be summarized using Clopper-Pearson methodology.



#### 12.5.1.4 Duration of Response (DOR)

Providing there are at least 5 responders overall, DOR will be summarized descriptively using the KM estimate, based on patients in the Disease Response Analysis Set with measurable disease who had a best overall response of confirmed CR or PR. Part B and Part C will be presented by Cycle 1 Day 1 total daily dose, whilst Part A is presented as an overall group only. The median, 25<sup>th</sup>, and 75<sup>th</sup> percentile of DOR and their two sided 95% CIs (Brookmeyer and Crowley, 1982) will be calculated where appropriate. The count and percent of responding patients who have an event or are censored will be summarized. Refer to [Section 10.4](#) for censoring rules.

DOR will also be presented graphically in the form of both a KM plot and a swimmer plot. Data will also be provided in a listing.

If there are less than 5 responders overall, DOR will be listed only.

#### 12.5.1.5 Radiographic Progression-Free Survival (PFS)

The All-Treated Analysis Set will be used for analysis of PFS. Part B and Part C will be presented by Cycle 1 Day 1 total daily dose, whilst Part A is presented as an overall group only. The number and percentage of patients with an event (PD or death) or are censored, along with reason of censoring will be presented. The censoring rules are described in [Section 10.4](#) and will be displayed as follows:

- Alive and Progression Free
- Withdrawal of Consent
- Lost to Follow-Up
- Lacking Disease Evaluation
- Alternative Anti-Cancer Therapy
- PD/Death After  $\geq 2$  Consecutive Missed Tumor Assessments

KM estimates together with the median, 25<sup>th</sup> and 75<sup>th</sup> percentile of survival time including their respective two-sided 95% CIs (Brookmeyer and Crowley, 1982) will be presented.

PFS will also be presented graphically in the form of both a KM plot and swimmer plot.

#### 12.5.1.6 Overall Survival (OS)

The secondary endpoint of OS is specified in the Protocol for Part B and Part C, though Part A is included as an exploratory endpoint described in [Section 12.6](#).

The All-Treated Analysis Set will be used for analysis of OS. Part B and Part C will be presented by Cycle 1 Day 1 total daily dose, whilst Part A is presented as an overall group only. The count and percentage of patients who have an event (death) or are censored will be summarized.

KM estimates for overall survival probability at 12 months along with its 95% CI based on the log(-log) method back transformed, together with associated statistics including the median, 25<sup>th</sup> and 75<sup>th</sup> percentile including their respective two-sided 95% CIs (Brookmeyer and Crowley, 1982) will be presented in addition to the arithmetic median duration of follow-up.

Overall survival will also be presented graphically in the form of a KM plot.

### 12.6 Exploratory Efficacy Analyses

There are no efficacy related exploratory, sensitivity or subgroup analyses planned per Protocol, however the following analyses will be provided;



- CBR<sub>24</sub> with Modification, based on the Clinically Evaluable Analysis Set, excluding patients unable to complete Cycle 1 due to reasons other than PD (discontinuation of treatment due to progression within one month of first dose) or toxicity (any discontinuation of treatment due to an AE within one month of first dose).
- CBR<sub>24</sub>, following the same methods described in [Section 10.4](#) based on the All-Treated Analysis Set.
- CBR<sub>24</sub>, following the same methods described in [Section 10.4](#) based on the Clinically Evaluable Analysis Set, by subgroup of ESR1 mutation status (Mutant, Wild Type, Unknown/Missing)
- CBR<sub>24</sub>, following the same methods described in [Section 10.4](#) based on the Clinically Evaluable Analysis Set, by subgroup of ESR1 mutation status (Mutant, Non-Mutant)
- CBR<sub>24</sub>, following the same methods described in [Section 10.4](#) based on the Clinically Evaluable Analysis Set, by subgroup of PIK3CA mutation status (PIK3CA mutant overall, PIK3CA H1047 mutant, PIK3CA other mutant, Wild Type, Unknown/Missing)
- ORR following the same methods described in [Section 12.5.1.1](#) based on the All-Treated Analysis Set.
- ORR following the same methods described in [Section 12.5.1.1](#) by subgroup of ESR1 mutation status (Mutant, Wild Type). The number of patients in the Disease Response Analysis Set with measurable disease in each subgroup will be used as the denominators for ORR.
- ORR following the same methods described in [Section 12.5.1.1](#) by subgroup of ESR1 mutation status (Mutant, Non-Mutant). The number of patients in the Disease Response Analysis Set with measurable disease in each subgroup will be used as the denominators for ORR.
- DCR for Part B and Part C, following the same methods described in [Section 12.5.1.3](#) for Part A.
- DCR following the same methods described in [Section 12.5.1.3](#) based on the All-Treated Analysis Set.
- PFS (KM Plot Only), following the same methods described in [Section 10.4](#) based on the All-Treated Analysis Set, by subgroup of PIK3CA mutation status (PIK3CA mutant overall, PIK3CA H1047 mutant, PIK3CA other mutant, Wild Type, Unknown/Missing)
- PFS (KM Plot Only), following the same methods described in [Section 10.4](#) based on the All-Treated Analysis Set, by C1D1 Initial Dose ( $\leq 120$ mg, 180/200mg,  $\geq 360$ mg) for Part A only.
- PFS (KM Plot Only), following the same methods described in [Section 10.4](#) based on the All-Treated Analysis Set, by Maximum Daily Dose ( $\leq 120$ mg, 180/200mg,  $\geq 360$ mg) for Part A only.
- PFS (KM Plot Only), following the same methods described in [Section 12.6](#) based on the All-Treated Analysis Set, for C1D1 doses (180/200 mg and 500 mg [including 250 mg BID] pooled across Part A and Part B.
- PFS (KM Plot Only), following the same methods described in [Section 10.4](#) based on the All-Treated Analysis Set, for C1D1 doses (200 mg QD and 500 mg QD) pooled across Part A and Part B.
- PFS (KM Plots Only), following the same methods described in [Section 10.4](#) based on the All-Treated Analysis Set, by subgroup of ESR1 mutation status (Mutant, Wild Type, Unknown/Missing) and dichotomized ESR1 mutation status (Mutant, Non-Mutant) presented as an overall dose group only, for Part A and Part B.
- PFS (KM Plots Only), following the same methods described in [Section 10.4](#) based on the All-Treated Analysis Set, by subgroup of ESR1 mutation status (Mutant, Wild Type, Unknown/Missing) and dichotomized ESR1 mutation status (Mutant, Non-Mutant) for C1D1 doses (180/200 mg vs. 500mg) pooled across Part A and Part B.
- OS for Part A (Overall only), following the same methods described in [Section 12.5.1.6](#) for Part B and Part C.

## 12.7 Safety Analyses

The All-Treated Analysis Set will be used for analysis of the safety endpoints. Tabulations will be generated separately for patients participating in Part A, Part B and Part C, by Cycle 1 Day 1 total daily dose. The safety endpoints are specified in [Section 7.1](#).



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## Adverse Events

All AEs recorded in the eCRFs will be coded using MedDRA (version 22.0 or higher) and graded using NCI CTCAE version 5.0. Summary tables will present counts and percentages of patients with events, unless otherwise specified.

The overall TEAE summary table will also be presented as an overall summary that combines Part A and Part B. These summaries will include line items for the following:

- All TEAEs
- Grade 3 or Higher TEAEs
- Treatment Related TEAEs
- Grade 3 or Higher Treatment Related TEAEs
- TEAEs with an Outcome of Death
- Serious TEAEs
- Serious Treatment Related TEAEs
- TEAEs Leading to Discontinuation of Study Treatment
- Treatment Related TEAEs Leading to Discontinuation of Study Treatment
- TEAEs Leading to an Interruption of Study Treatment
- Treatment Related TEAEs Leading to an Interruption of Study Treatment
- TEAEs Leading to a Dose Reduction
- TEAEs Leading to Discontinuation of Study

Further, the number and percentage of patients with the following types of TEAEs will be summarized by system organ class (SOC), preferred term (PT) and maximum CTCAE grade:

- First Cycle DLTs (based on the DLT Analysis Set)
- TEAEs
- Treatment Related TEAEs
- TEAEs Leading to Discontinuation of Study Treatment
- Treatment Related TEAEs Leading to Discontinuation of Study Treatment
- TEAEs Leading to an Interruption of Study Treatment
- Treatment Related TEAEs Leading to an Interruption of Study Treatment
- TEAEs Leading to a Dose Reduction of Study Treatment
- Serious TEAEs
- Serious Treatment Related TEAEs

In addition, the number and percentage of patients with the following types of TEAEs will be summarized by PT only.

- TEAEs
- Treatment Related TEAEs
- TEAEs Based on the Standard MedDRA Query (SMQ) for “Torsade de Pointes/QT Prolongation” or Seizure

Separate listings will be provided for TEAEs, non-TEAEs, Serious TEAEs and TEAEs based on the SMQ for “Torsade de Pointes/QT Prolongation” or Seizure.

## Deaths

TEAEs that led to death will be summarized by PT only. The following summaries will be presented:

- TEAEs with an Outcome of Death

An additional summary presenting all cause death will be presented, displaying the primary cause of death and the number of deaths within/after 30 days of the last study medication.

All TEAEs that led to death, and all primary causes of death will be presented in separate listings.

## Laboratory Data

Laboratory data will be analyzed in System International (SI) units.



NCI CTCAE v5.0 grades will be applied for selected hematology and chemistry parameters, indicated in [Table 2](#) by the notation of Low, High, High or Low or Grade 1.

Grades are applied based only on the numeric SI value of the parameter assessed; clinical signs and symptoms are not considered. Where categories are only distinguished by clinical signs or symptoms, the lowest of the possible grades will be assigned.

Unscheduled laboratory measurements will be included in the analysis of the worst grade for NCI-CTCAE gradable parameters.

#### 12.7.1.1 Hematology and Clinical Chemistry

Selected parameters will be graded by NCI-CTCAE version 5.0, refer to [Table 2](#) in [Section 10.6](#) for the full list of protocol required parameters, including those selected for CTCAE grading.

Descriptive summaries of the baseline toxicity grade and worst post-baseline toxicity grade will be summarized, in addition to shifts from baseline to worst post-baseline will also be presented.

Hematology and clinical chemistry parameters will be listed separately, with associated NCI-CTCAE grades and normal ranges also displayed.

#### 12.7.1.2 Coagulation

Refer to [Table 2](#) in [Section 10.6](#) for a list of protocol required coagulation parameters. Coagulation data will be listed only.

#### 12.7.1.3 Urinalysis

Refer to [Table 2](#) in [Section 10.6](#) for a list of protocol required urinalysis parameters. Urinalysis data will be listed only.

#### 12.7.1.4 Other Laboratory Parameters

All other laboratory parameters collected in this study will be listed displaying all information collected on eCRF. Refer to [Table 2](#) in [Section 10.6](#) for a list of protocol required other laboratory parameters.

### Vital Signs

The absolute value, change from baseline and percentage change from baseline will be summarized descriptively for Pulse Rate only, by dose cohort and overall at each scheduled visit.

All other vital signs data will be listed only.

### Other Observations Related to Safety

#### 12.7.1.5 Physical Examinations

All complete and abbreviated physical examinations will be listed.

#### 12.7.1.6 Electrocardiogram

The screening electrocardiogram (ECG) will be a single 12-lead ECG. At all other visits, at each time point, triplicate 12-lead ECGs will be performed. This set of triplicate ECGs are recorded across both Scheduled and Unscheduled visit pages of the eCRF. Scheduled and Unscheduled results at a given visit will be programmatically identified using the protocol specified time windows around the associated visit dosing time, without consideration for position (sitting/supine). The average of the windowed values will be used for analyses of ECG tables.



The time windows applied for identification of ECGs at each time point within a given visit are;

- Pre-Dose: Any result prior to the dosing time
- 2 hrs Post-Dose:  $\pm$  15 minutes 2 hours post dosing time
- 4 hrs Post-Dose:  $\pm$  25 minutes 4 hours post dosing time

The absolute value and change from baseline value of each ECG parameter [Heart Rate (beats/min), PR Interval (msec), QRS duration (msec), QT interval (msec), QTcB (msec) and QTcF (msec)] will be summarized descriptively at each scheduled visit.

Overall interpretation of ECG will be presented by result category (Normal, Abnormal, Unevaluable and Unknown) at each scheduled visit.

The absolute and change from baseline values for QTc intervals will be further summarized categorically at each scheduled visit, as detailed below. A shift table for the absolute values from baseline to worst post baseline will also be presented.

| Absolute Values                                                                                                                                                                                                  | Change from Baseline                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• &lt; 450 msec</li><li>• <math>\geq</math> 450 msec to &lt; 480 msec</li><li>• <math>\geq</math> 480 msec to &lt; 500 msec</li><li>• <math>\geq</math> 500 msec</li></ul> | <ul style="list-style-type: none"><li>• &lt; 30 msec</li><li>• <math>\geq</math> 30 msec to &lt; 60 msec</li><li>• <math>\geq</math> 60 msec</li></ul> |

The 12-lead ECG data will also be listed.

12.7.1.7 Echocardiogram

Echocardiograms (ECHOs) will be listed only.

12.7.1.8 ECOG Performance Status

Baseline ECOG performance status will be summarized as part of the baseline characteristics, all ECOG data will be listed. The grading of ECOG performance status is defined in [Section 10.6](#).

**Biomarkers**

Additional exploratory biomarker analyses in ctDNA and tumor tissue will be analyzed in a separate plan if sufficient data are available. The following sections describe these other analyses within the context of this SAP.

12.7.1.9 ESR1 and PIK3CA Mutation Status

Selected efficacy analyses will be performed based on ESR1 mutation status (Mutant, Wild Type, Unknown/Missing) and PIK3CA mutation status (PIK3CA Mutant [H1047, Other, Overall], Wild Type, Unknown/Missing). See [Section 12.6](#) for further details. Both ESR1 and PIK3CA mutation status' will also be listed.

12.7.1.10 ctDNA

Results for ctDNA will be listed only.

12.8 Pharmacokinetic Analyses

The pharmacokinetic analyses will be performed on all patients in the appropriate PK Analysis Sets, presented by their initial dose group (see [Section 12.0](#)).



## Dealing with Concentrations Below the Lower Limit of Quantification (BLOQ)

For all calculations, figures and estimation of individual PK parameters, all concentrations assayed as BLOQ should be set to zero irrespective of where they occur within a profile. Individual BLOQ results occurring between two quantifiable concentrations may be identified by the pharmacokineticist as anomalous concentrations. Results reported as NRR (No Recorded Result) will be set to missing.

In log-linear plots these values would not be represented. In the tables presenting summary statistics of concentration-time series, the total number of values (n) and the number of values that are above the lower limit of quantification (LLOQ) should be presented to allow appropriate interpretation of the data.

A statement similar to “all values reported as BLOQ have been replaced with zero” should be included as a footnote to the appropriate tables and figures.

If the majority of concentrations within an initial dose group are BLOQ, the pharmacokineticist may choose to not report any parameters for the data in question. Alternatively, if most patients have at least one quantifiable result, it may be informative to report and summarize some limited PK parameters:

- If all concentrations in a profile are BLOQ,  $C_{max}$  and  $AUC_{last}$  may be reported as zero ( $T_{max}$  is missing).
- A minimum of 3 quantifiable concentrations is recommended to report  $AUC_{last}$  (except  $AUC_{last}$  may be reported as zero when all concentrations are zero as noted above).
- AUCs that represent a specified time interval, such as  $AUC_{tau}$ , should generally only be reported at the discretion of pharmacokineticist if:
  - Concentrations after  $C_{max}$  remain quantifiable to the end of the interval ( $T_{last}$  is  $\geq \tau$ ), or
  - AUC to the end of the interval can be extrapolated based on  $t_{1/2}$  (with extrapolation  $\leq 20\%$ ), or
  - Concentrations remain quantifiable through the last sample before the end of the interval, and the additional AUC from that time ( $T_{last}$ ) to the “zero” concentration at the end of the interval is less than 20% of the total AUC.

## Missing Values

Summary statistics should represent the central tendency of the data and, as such, should not be reported if a substantial portion of the data are missing (e.g., if data for 50% or more of the observations within a group are missing) unless appropriate cautions and rationale are provided in the study report. This recommendation applies to both concentration-time data summarized by nominal time point, and to PK parameters summarized within an initial dose group.

## Plasma Concentrations

Descriptive statistics (number of patients, number of patients with a value above lower limit of quantification; mean, geometric mean, STD, coefficient of variation [%CV], median, min, and max) will be presented by Study Part, Dose, Cycle and each nominal time point. Patients who had dose modifications different from the planned dose at specific days will be excluded from the concentration summary at the corresponding days. In addition, any individual concentration (with the exception of Cycle 1 Day 1) that does not meet the steady state criteria (See [Section 10.7](#)) will also be excluded from the concentration summaries.

Time deviations will be listed with a flag for all deviations that are considered to be “significant”. The default is that all samples with an absolute value of time deviation  $>10\%$  will be flagged and samples with a time deviation  $>20\%$  will be treated as missing for the calculation of concentration summary statistics by nominal time point. These default percentages may be reconsidered when appropriate based on the PK profile for the particular drug under consideration.

- Time Deviation (%) =  $((\text{Actual Time} - \text{Planned Time}) / \text{Planned Time}) * 100$

The following plots will be presented for concentrations of ARV-471 and ARV-473 for Study Part A and Part C (Cohorts C1 - C4) and Palbociclib for Study Part C (Cohorts C1 - C4).



- Linear (+/-SD) and semi-logarithmic plots of the arithmetic mean (+SD) plasma concentration by scheduled sampling time will be provided by Study Part, Cycle, Day, and Dose. These plots will show time in hours and will present all calculated means up to 24 hours post-dose where applicable.
- Linear and semi-logarithmic plots of the median plasma concentration by scheduled sampling time will be provided by Study Part, Cycle, Day, and Dose. These plots will show time in hours and will present all calculated medians up to 24 hours post-dose where applicable.
- Linear and semi-logarithmic plots of the individual plasma concentration by actual time post dose will be provided by patient (one patient per page) with Cycle 1 Day 1 and Cycle 1 Day 15 overlaid. These plots will show time in hours.
- Linear (+/-SD) plots of the arithmetic mean Predose plasma concentrations by scheduled study day will be provided by initial dose group for Part A, Part B, and Part C. These plots will show time in days.
- Linear plots of the median Predose plasma concentrations by scheduled study day will be provided by initial dose group for Part A, Part B, and Part C. These plots will show time in days.

The following plots will be presented for concentrations of ARV-471, ARV-473 and Palbociclib, for Study Part C (Cohort C5 Only).

- Linear (+/-SD) and semi-logarithmic plots of the arithmetic mean (+SD) plasma concentration by scheduled sampling time will be provided for Palbociclib at Cycle 1 Day 8 and Cycle 1 Day 21 or Cycle 2 Day 15 (visits overlaid), and ARV-471 and ARV-473 at Cycle 1 Day 21 or Cycle 2 Day 15 overlaid. These plots will show time in hours will present all calculated means up to 24 hours post-dose where applicable.
- Linear and semi-logarithmic plots of the median plasma concentration by scheduled sampling time will be provided for Palbociclib at Cycle 1 Day 8 and Cycle 1 Day 21 or Cycle 2 Day 15 (visits overlaid), and ARV-471 and ARV-473 at Cycle 1 Day 21 or Cycle 2 Day 15 overlaid. These plots will show time in hours and will present all calculated medians up to 24 hours post-dose where applicable.
- Linear and semi-logarithmic plots of the individual plasma concentration by actual time post dose will be provided by patient (overlaid on one page), with C1D8 and C1D21 (or C2D15) overlaid for palbociclib and C1D21 (or C2D15) for ARV-471 and ARV-473 (one analyte per page). These plots will show time in hours.

All individual plasma concentration data will be listed by patient.

### Plasma Pharmacokinetic Parameters

Population PK analyses will be reported separately by the sponsor, these analyses are not covered by this SAP.

PK parameters including but not limited to those indicated in



Table 4 will be estimated by using non-compartmental methods with WinNonlin® (Version 8.1). The AUCs will be calculated using linear trapezoidal linear interpolation method.

Actual PK sampling times will be used in the derivation of PK parameters. Actual time for nominal pre-dose samples will be set to zero for PK parameter calculations and individual concentration-time plots, unless the actual time occurs after the dose. Nominal PK sampling times may be used if the actual PK times are not recorded. If the actual time is missing, the scheduled time will be substituted and flagged. All PK parameter results are included in summary tables, regardless of any time deviation for the corresponding sample.

If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (not calculated). Note that NC values will not be generated beyond the day that a patient discontinues from the study.

In summary tables, statistics will not be presented for a particular initial dose group if more than 50% of the data are NC.

**Table 4 Non-Compartmental PK Parameters**

| Study Part, Visit                                                                                                                              | ARV-471 PK Parameters <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | ARV-473 PK Parameters <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Sum of ARV-471 and ARV-473 <sup>a, c</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Palbociclib PK Parameters <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Part A and Part C (Cohorts C1 - C4)<br>Cycle 1 Day 1                                                                                           | <ul style="list-style-type: none"> <li>C<sub>max</sub></li> <li>T<sub>max</sub></li> <li>T<sub>last</sub></li> <li>AUC<sub>last</sub></li> <li>AUC<sub>tau</sub></li> <li>C<sub>max</sub> (dn)</li> <li>AUC<sub>tau</sub> (dn)</li> <li>AUC<sub>last</sub> (dn)</li> </ul>                                                                                                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>C<sub>max</sub></li> <li>T<sub>max</sub></li> <li>T<sub>last</sub></li> <li>AUC<sub>last</sub></li> <li>AUC<sub>tau</sub></li> <li>MRC<sub>max</sub> <sup>b</sup></li> <li>MRAUC<sub>tau</sub> <sup>b</sup></li> <li>C<sub>max</sub> (dn)</li> <li>AUC<sub>tau</sub> (dn)</li> <li>AUC<sub>last</sub> (dn)</li> </ul>                                                                                                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>C<sub>max</sub></li> <li>T<sub>max</sub></li> <li>T<sub>last</sub></li> <li>AUC<sub>last</sub></li> <li>AUC<sub>tau</sub></li> <li>C<sub>max</sub> (dn)</li> <li>AUC<sub>tau</sub> (dn)</li> <li>AUC<sub>last</sub> (dn)</li> </ul>                                                                                                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>C<sub>max</sub></li> <li>T<sub>max</sub></li> <li>T<sub>last</sub></li> <li>AUC<sub>last</sub></li> <li>AUC<sub>tau</sub></li> <li>C<sub>max</sub> (dn)</li> <li>AUC<sub>tau</sub> (dn)</li> <li>AUC<sub>last</sub> (dn)</li> </ul>                                                                                                                                                                                                                                                                                                                                                          |
| Part A and Part C (Cohorts C1 - C4)<br>Cycle 1 Day 15<br><br>Part C (Cohort C5 Only)<br>Cycle 1 Day 8<br>Cycle 1 Day 21 (or<br>Cycle 2 Day 15) | <ul style="list-style-type: none"> <li>C<sub>max</sub></li> <li>C<sub>min</sub> <sup>b</sup></li> <li>T<sub>max</sub></li> <li>T<sub>last</sub></li> <li>AUC<sub>last</sub></li> <li>AUC<sub>tau</sub></li> <li>AUC<sub>0-24</sub> <sup>b</sup></li> <li>Rac(C<sub>max</sub>) <sup>b</sup></li> <li>Rac(AUC<sub>tau</sub>) <sup>b</sup></li> <li>Effective T<sub>1/2</sub> <sup>b</sup></li> <li>C<sub>trough</sub> <sup>b</sup></li> <li>C<sub>av</sub> <sup>b</sup></li> <li>CL/F</li> <li>V<sub>d</sub>/F</li> <li>PTF</li> <li>C<sub>max</sub> (dn)</li> <li>AUC<sub>tau</sub> (dn)</li> <li>AUC<sub>last</sub> (dn)</li> </ul> | <ul style="list-style-type: none"> <li>C<sub>max</sub></li> <li>C<sub>min</sub> <sup>b</sup></li> <li>T<sub>max</sub></li> <li>T<sub>last</sub></li> <li>AUC<sub>last</sub></li> <li>AUC<sub>tau</sub></li> <li>AUC<sub>0-24</sub> <sup>b</sup></li> <li>MRC<sub>max</sub> <sup>b</sup></li> <li>MRAUC<sub>tau</sub> <sup>b</sup></li> <li>Rac(C<sub>max</sub>) <sup>b</sup></li> <li>Rac(AUC<sub>tau</sub>) <sup>b</sup></li> <li>Effective T<sub>1/2</sub> <sup>b</sup></li> <li>C<sub>trough</sub> <sup>b</sup></li> <li>C<sub>av</sub> <sup>b</sup></li> <li>CL/F</li> <li>V<sub>d</sub>/F</li> <li>PTF</li> <li>C<sub>max</sub> (dn)</li> <li>AUC<sub>tau</sub> (dn)</li> <li>AUC<sub>last</sub> (dn)</li> </ul> | <ul style="list-style-type: none"> <li>C<sub>max</sub></li> <li>C<sub>min</sub> <sup>b</sup></li> <li>T<sub>max</sub></li> <li>T<sub>last</sub></li> <li>AUC<sub>last</sub></li> <li>AUC<sub>tau</sub></li> <li>AUC<sub>0-24</sub> <sup>b</sup></li> <li>Rac(C<sub>max</sub>) <sup>b</sup></li> <li>Rac(AUC<sub>tau</sub>) <sup>b</sup></li> <li>Effective T<sub>1/2</sub> <sup>b</sup></li> <li>C<sub>trough</sub> <sup>b</sup></li> <li>C<sub>av</sub> <sup>b</sup></li> <li>CL/F</li> <li>V<sub>d</sub>/F</li> <li>PTF</li> <li>C<sub>max</sub> (dn)</li> <li>AUC<sub>tau</sub> (dn)</li> <li>AUC<sub>last</sub> (dn)</li> </ul> | <ul style="list-style-type: none"> <li>C<sub>max</sub></li> <li>C<sub>min</sub> <sup>b</sup></li> <li>T<sub>max</sub></li> <li>T<sub>last</sub></li> <li>AUC<sub>last</sub></li> <li>AUC<sub>tau</sub></li> <li>AUC<sub>0-24</sub> <sup>b</sup></li> <li>Rac(C<sub>max</sub>) <sup>b</sup></li> <li>Rac(AUC<sub>tau</sub>) <sup>b</sup></li> <li>Effective T<sub>1/2</sub> <sup>b</sup></li> <li>C<sub>trough</sub> <sup>b</sup></li> <li>C<sub>av</sub> <sup>b</sup></li> <li>CL/F</li> <li>V<sub>d</sub>/F</li> <li>PTF</li> <li>C<sub>max</sub> (dn)</li> <li>AUC<sub>tau</sub> (dn)</li> <li>AUC<sub>last</sub> (dn)</li> </ul> |

<sup>a</sup>. Reported if data permits<sup>b</sup>. Reported using programming (SAS) approach<sup>c</sup>. At the request of Arvinas clinical pharmacology lead

For patients on QD dosing schedule pre-dose plasma concentrations on Cycle 1 Day 2 will be used for 24 hour post dose on Cycle 1 Day 1 for the purpose of calculating PK parameters. For Study Part A and Part C (Cohorts C1 - C4) plasma concentrations 24 hour post dose on Cycle 1 Day 15 will be assumed to be the same as pre-dose plasma concentrations on Cycle 1 Day 15 for the purpose of calculating AUC<sub>tau</sub> parameters. For Study Part C (Cohort C5 Only), plasma concentrations 24 hour post dose on Cycle 1 Day 8 and either Cycle 1 Day 21 or Cycle 2 Day 15 will be assumed to be the same as pre-dose plasma concentrations on Cycle 1 Day 8 and either Cycle 1 Day 21 or Cycle 2 Day 15, respectively, for the purpose of calculating AUC<sub>tau</sub> parameters.

For patients on BID dosing schedule, only AUC<sub>last</sub> will be reported for Cycle 1 Day 1. Plasma concentrations 12 hour post dose on Cycle 1 Day 15 will be assumed to be the same as pre-dose plasma concentrations on Cycle 1 Day 15 for the purpose of calculating AUC<sub>tau</sub> parameters. BID Dosing Cohorts estimate for AUC<sub>0-24</sub> is estimated as AUC<sub>tau</sub> multiplied by 2 for Cycle 1 Day 15. When needed C<sub>max</sub>, T<sub>max</sub>, T<sub>last</sub> and AUC<sub>last</sub> will be calculated without the above modifications.

**Table 5 Plasma Pharmacokinetic Parameters**

| Parameter <sup>a</sup>                      | Description                                                                                                                                                                                                                                                                                                                                                   | SAS Programming Notes                                                                                                                                                                                 | Summary Statistic Reporting Precision <sup>b</sup> |
|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| C <sub>max</sub>                            | Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units                                                                                                                                                                                        | C <sub>max</sub> from WNL                                                                                                                                                                             | 5 sd.                                              |
| C <sub>min</sub>                            | Minimum observed plasma concentration                                                                                                                                                                                                                                                                                                                         | Calculated in SAS                                                                                                                                                                                     | 5 sd.                                              |
| T <sub>max</sub>                            | Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.                                                                                                                                                                    | T <sub>max</sub> from WNL                                                                                                                                                                             | 2 dp.                                              |
| T <sub>last</sub>                           | Time of last measurable observed concentration                                                                                                                                                                                                                                                                                                                | T <sub>last</sub> from WNL                                                                                                                                                                            | 2 dp.                                              |
| AUC <sub>last</sub>                         | Area under the concentration-time curve (time 0 to time of last quantifiable concentration post dose).                                                                                                                                                                                                                                                        | AUC <sub>last</sub> from WNL                                                                                                                                                                          | 5 sd.                                              |
| AUC <sub>tau</sub>                          | Area under the concentration-time curve over the dosing interval.<br>For QD dosing schedule, tau=24 hr; for BID dosing schedule, tau=12 hr.                                                                                                                                                                                                                   | AUC <sub>tau</sub> from WNL                                                                                                                                                                           | 5 sd.                                              |
| AUC <sub>0-24</sub>                         | Area under the concentration-time curve over 24 hours at steady state.<br>For QD, AUC <sub>0-24</sub> =AUC <sub>tau</sub><br>For BID dosing, AUC <sub>0-24</sub> = AUC <sub>tau</sub> *2.                                                                                                                                                                     | Calculated from SAS                                                                                                                                                                                   | 5 sd.                                              |
| MRC <sub>max</sub>                          | Epimer ARV-473 to parent molar ratio of C <sub>max</sub><br>Molar weight of ARV-471 and ARV-473 is equivalent                                                                                                                                                                                                                                                 | ARV-473 C <sub>max</sub> / ARV-471 C <sub>max</sub><br>calculated in SAS                                                                                                                              | 3 sd.                                              |
| MRAUC <sub>tau</sub>                        | Epimer ARV-473 to parent molar ratio of AUC <sub>tau</sub><br>Tau is the dosing interval of 24hr for QD dosing schedule, Tau will be 12 hr for BID dosing schedule.<br><br>Molar weight of ARV-471 and ARV-473 is equivalent                                                                                                                                  | ARV-473 AUC <sub>tau</sub> / ARV-471 AUC <sub>tau</sub><br>calculated in SAS<br><br>Note: parameter is only calculated if neither parent nor metabolite AUC <sub>tau</sub> are flagged for exclusion. | 3 sd.                                              |
| Rac(C <sub>max</sub> )                      | Accumulation index (ratio) for C <sub>max</sub> .                                                                                                                                                                                                                                                                                                             | C <sub>max</sub> (Day 15) / C <sub>max</sub> (Day 1)<br>calculated in SAS                                                                                                                             | 3 sd.                                              |
| Rac(AUC <sub>tau</sub> )                    | Accumulation index (ratio) for AUC <sub>tau</sub> . Tau is the dosing interval of 24hr for QD dosing schedule, Tau will be 12 hr for BID dosing schedule                                                                                                                                                                                                      | AUC <sub>tau</sub> (Day 15) / AUC <sub>tau</sub> (Day 1)<br>calculated in SAS<br><br>Note: parameter is only calculated if Day 1 AUC <sub>tau</sub> is not flagged for exclusion.                     | 3 sd.                                              |
| EFF_T-HALF<br>(Effective T <sub>1/2</sub> ) | Effective half-life based on accumulation ratio of AUC <sub>tau</sub> expressed in time units.<br>EFF_T-HALF, will be calculated as $\text{Tau} * \ln(2) / \ln(\text{Rac}(\text{AUC}_{\text{tau}}) / [\text{Rac}(\text{AUC}_{\text{tau}}) - 1])$ , where Tau is the dosing interval of 24hr for QD dosing schedule, Tau will be 12 hr for BID dosing schedule | $\text{Tau} * \ln(2) / \ln(\text{Rac}(\text{AUC}_{\text{tau}}) / [\text{Rac}(\text{AUC}_{\text{tau}}) - 1])$ calculated in SAS                                                                        | 3 sd.                                              |
| C <sub>trough</sub>                         | Trough (Pre-dose) concentration                                                                                                                                                                                                                                                                                                                               | Calculated in SAS                                                                                                                                                                                     | 5 sd.                                              |



|              |                                                                                                                                                                                                                                                    |                                   |       |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------|
| Cav          | Average concentration: $Cav = AUC_{tau}/Tau$ , where Tau is the dosing interval of 24hr for QD dosing or 12 hr for BID dosing.                                                                                                                     | Calculated in SAS                 | 5 sd. |
| CL/F         | Apparent clearance at steady state.                                                                                                                                                                                                                | CLss_F from WNL                   | 3 sd. |
| Vd/F         | Apparent volume of distribution at steady state.                                                                                                                                                                                                   | Vz_F from WNL                     | 3 sd. |
| PTF          | Peak:Trough Fluctuation, defined as $(C_{max} - C_{min})/Cav$ , where $Cav = AUC_{tau}/Tau$ , Tau is the dosing interval of 24hr for QD dosing schedule, Tau will be 12 hr for BID dosing schedule.<br>This is FI from Table 16 of ARV-471-mBC-101 | Fluctuation% from WNL             | 3 sd. |
| Cmax (dn)    | Dose normalized Cmax                                                                                                                                                                                                                               | Cmax/Dose<br>Calculated in SAS    |       |
| AUCtau (dn)  | Dose normalized AUCtau                                                                                                                                                                                                                             | AUCtau/Dose<br>Calculated in SAS  |       |
| AUClast (dn) | Dose normalized AUClast                                                                                                                                                                                                                            | AUClast/Dose<br>Calculated in SAS |       |

<sup>a</sup> If data permits

<sup>b</sup> dp.=Decimal Places; sd.=Significant Digits.

Flag will be created for  $AUC_{last}$  if  $T_{last}$  is not equal to 8 hours.

Descriptive statistics (number of patients, mean, STD, geometric mean, %CV, median, min, and max) will be used to summarize the calculated PK parameters by initial dose group and day. For  $T_{max}$  and  $T_{last}$ , only median, min and max will be presented.

Scatter plots of individual PK parameters  $C_{max}$  and  $AUC_{tau}$  (plus geometric means) by initial dose group for each analyte will be provided for Study Part A and Part C (Cohorts C1 - C4) for Cycle 1 Day 1 and Cycle 1 Day 15 Tau is the dosing interval of 24hr for QD dosing schedule; tau will be 12 hr for BID dosing schedule.

Additionally for Study Part C (Cohort C5 Only), boxplots of individual PK parameters  $C_{max}$  and  $AUC_{tau}$  (plus geometric means) for Palbociclib at Cycle 1 Day 8 and Cycle 1 Day 21 (or Cycle 2 Day 15) and for ARV-471 and ARV-473 at Cycle 1 Day 21 (or Cycle 2 Day 15) will also be presented.

Patients who had dose modifications different from the planned dose at specific days will be excluded from the PK parameter summaries at the corresponding days. In addition, any PK parameter derived from an individual concentration (with the exception of Cycle 1 Day 1) that does not meet the steady state criteria (See [Section 10.7](#)) will also be excluded from the concentration summaries.

All parameters will be listed by patient, within study part, initial dose group and day. A separate listing will be provided for PK Parameter comments.

**Statistical Analysis of Drug-Drug Interaction in Study Part C (Cohort C5 Only)**

Potential drug-drug interaction effect of ARV-471 on Palbociclib will be evaluated by comparing the exposures ( $C_{max}$  and  $AUC_{tau}$ ) of Palbociclib on Cycle 1 Day 8 and Cycle 1 Day 21 (or Cycle 2 Day 15).

A linear mixed effect model will be performed on the log-transformed PK parameters. The model will include visit (Cycle 1 Day 8, Cycle 1 Day 21/Cycle 2 Day 15) as the fixed effect and patients as a random effect. Estimates of the adjusted geometric mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted geometric mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Palbociclib administered alone on Cycle 1 Day 8 will be the reference treatment and Palbociclib co-administered with ARV-471 on Cycle 1 Day 21 (or Cycle 2 Day 15) will be the test treatment.

The patients who had dose modifications different from the planned dose for Palbociclib will be excluded from the analysis at the corresponding days (dose modifications for ARV-471 will still be included). In addition, only patients with Palbociclib concentrations meeting steady state at Cycle 1 Day 8 and Cycle 1 Day 21/Cycle 2 Day 15 and ARV-471 concentrations meeting steady state at Cycle 1 Day 21/Cycle 2 Day 15 will contribute to this analysis.



### PK-PD Analysis

PK-PD modeling will be attempted to investigate any causal relationship between ARV-471 exposure (including its active moieties, if appropriate) and biomarker, efficacy, safety, antitumor activity, and/or laboratory data. These modeling analyses will be reported separately by sponsor from the CSR.



13.0 References

**Rossi L [et al.]** Clinical outcomes after palbociclib with or without endocrine therapy in postmenopausal women with hormone receptor positive and HER2-negative metastatic breast cancer enrolled in the TREnd trial [Journal]. - [s.l.] : Breast Cancer Res, 2019. - 1 : Vol. 21.

**Turner NC [et al.]** Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer [Journal]. - [s.l.] : N Engl J Med, 2015. - 3 : Vol. 373.

14.0 Appendix 1: Glossary of Abbreviations

| Glossary of Abbreviations: |                                                                                                                               |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| %CV                        | Coefficient of Variation                                                                                                      |
| AE                         | Adverse Event                                                                                                                 |
| AI                         | Aromatase Inhibitor                                                                                                           |
| ALP                        | Alkaline Phosphatase                                                                                                          |
| ALT                        | Alanine Aminotransferase                                                                                                      |
| AST                        | Aspartate aminotransferase                                                                                                    |
| ATC                        | Anatomic Therapeutic Classification                                                                                           |
| aPTT                       | Activated Partial Thromboplastin Time                                                                                         |
| AUC                        | Area Under the Plasma Concentration Time Curve                                                                                |
| AUC <sub>0-last</sub>      | AUC from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation |
| AUC <sub>0-tau</sub>       | AUC from time zero during a dosing interval, calculated by linear up/log down trapezoidal summation                           |
| BLOQ                       | Below the Limit of Quantification                                                                                             |
| BMI                        | Body Mass Index                                                                                                               |
| BUN                        | Blood Urea Nitrogen                                                                                                           |
| CBR                        | Clinical Benefit Rate                                                                                                         |
| CDK                        | Cyclin-Dependent Kinase                                                                                                       |
| CI                         | Confidence Interval                                                                                                           |
| CKD-EPI                    | Chronic Kidney Disease Epidemiology                                                                                           |
| CL/F                       | Apparent Oral Plasma Clearance                                                                                                |
| C <sub>max</sub>           | Maximum Concentration, obtained directly from the observed concentration versus time data                                     |
| CMO                        | Chief Medical Officer                                                                                                         |
| CR                         | Complete Response                                                                                                             |
| CRC                        | Cohort Review Committee                                                                                                       |
| CRF                        | Case Report Form                                                                                                              |
| CSR                        | Clinical Study Report                                                                                                         |
| CT                         | Computed Tomography                                                                                                           |
| ctDNA                      | Circulating Tumor Deoxyribonucleic Acid                                                                                       |
| CTMS                       | Clinical Trial Management System                                                                                              |



|                          |                                                                        |
|--------------------------|------------------------------------------------------------------------|
| DLT                      | Dose-Limiting Toxicity                                                 |
| DOR                      | Duration of Response                                                   |
| ECG                      | Electrocardiogram                                                      |
| ECHO                     | Echocardiogram                                                         |
| ECOG                     | Eastern Cooperative Oncology Group                                     |
| eCRF                     | Electronic Case Report Form                                            |
| EOT                      | End of Treatment                                                       |
| ER                       | Estrogen Receptor                                                      |
| ER+/HER2-                | Estrogen Receptor Positive/Human Epidermal Growth Factor Receptor 2    |
| ESR1                     | Estrogen Receptor 1                                                    |
| INR                      | International Normalized Ratio                                         |
| KM                       | Kaplan-Meier                                                           |
| LLOQ                     | Lower Limit of Quantification                                          |
| mBC                      | Metastatic Breast Cancer                                               |
| MedDRA                   | Medical Dictionary for Regulatory Activities                           |
| MRAUC <sub>(0-tau)</sub> | ARV-473 to ARV-471 ratio for AUC <sub>0 tau</sub>                      |
| MRC <sub>max</sub>       | ARV-473 to ARV-471 ratio for C <sub>max</sub>                          |
| MRI                      | Magnetic Resonance Imaging                                             |
| MTD                      | Most Tolerated Dose                                                    |
| NC                       | Not Calculated                                                         |
| NCI CTCAE                | National Cancer Institute Common Terminology Criteria Adverse Event    |
| NE                       | Not Evaluable                                                          |
| NRR                      | No Recorded Result                                                     |
| ORR                      | Overall Response Rate                                                  |
| OS                       | Overall Survival                                                       |
| PD                       | Progressive Disease                                                    |
| PE                       | Physical Examination                                                   |
| PFS                      | Progression-Free Survival                                              |
| PIK3CA                   | Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha |
| PK                       | Pharmacokinetic                                                        |
| PR                       | Partial Response                                                       |
| PT                       | Preferred Term                                                         |
| QTcB                     | Corrected QT Interval by Bazett's Method                               |
| QTcF                     | Corrected QT Interval by Fredericia's Method                           |
| RECIST                   | Response Evaluations Criteria in Solid Tumors                          |
| RP2D                     | Recommended Phase 2 Dose                                               |
| SABCS                    | San Antonio Breast Cancer Symposium                                    |



|                  |                                           |
|------------------|-------------------------------------------|
| SAP              | Statistical Analysis Plan                 |
| SD               | Stable Disease                            |
| SERD             | Selective Estrogen Receptor Degraders     |
| SERM             | Selective Estrogen Receptor Modulators    |
| SMQ              | Standard MedDRA Query                     |
| SOC              | System Organ Class                        |
| SRC              | Safety Review Committee                   |
| STD              | Standard Deviation                        |
| TEAE             | Treatment Emergent Adverse Events         |
| TLFs             | Tables, Listings and Figures              |
| T <sub>max</sub> | Time to C <sub>max</sub>                  |
| ULN              | Upper Limit of Normal                     |
| USPI             | United States Prescribing Information     |
| Vd/F             | Apparent Volume of Distribution           |
| WHODD            | World Health Organization Drug Dictionary |