Protocol C4891016

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

Statistical Analysis Plan
(SAP)

Version: 3

Date: 25 May 2023

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 08 Apr 2022	Amendment 1 25 Mar 2022	NA	NA
2 25 Nov 2022	Amendment 2 21 Oct 2022	Section 2, 2.2, 2.3, 3.1, 5.1.1 Section 6.5.1 Section 6.5.3	Modified according to protocol amendment. Clarified that the duration since primary diagnosis is summarized and added the definition. Corrected definition of duration of exposure.
3 25 May 2023	Amendment 2 21 Oct 2022	Section 6.2.3.2 Section 6.2.4.1 Section 6.5.4.1 Section 6.5.4.2 Throughout the SAP	Added the details of calculation of within-patient average C_{trough}. Removed the word "exact" to use Wilson's score method for the 95% CI. Added that absolute values of vital signs are summarized. Added that absolute values of ECG parameters are summarized. Corrected typographical errors and made minor edits.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4891016. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. This SAP was written in reference to the protocol amendment 2 dated 21 October 2022.

Note: in this document any text taken directly from the protocol is *italicized*.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

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

Type	Objective	Endpoint.	Est.imand
		• *Time to event end_oints: PFS, DOR*	
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2.2.1. Primary Estimand(s)

The prima1y estimand is defined by the following attributes:

- *Population: participants who receives at least 1 dose and classified as DLT-evaluable, ie, participants who experiences a DLT or in the absence of a DLT, receives at least 75% of the planned dose intensity of study intervention during the DLT window.*
- *Endpoint: occurrence of DLTs at first cycle.*
- *Treatment condition: Participants who fail to complete at least 75% of study drug treatment in Cycle 1 for reasons other than DLT (eg, logistical or technical reasons, non-DLT-related dose delays) are considered not to be DLT-evaluable and will be replaced.*
- *Population-level summary: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT-evaluation period divided by the number of DLT-evaluable participants in the DLT-evaluation period.*

2.3. Study Design

This study is a single-country, non-randomized, open-label, Phase 1 study. This study will evaluate the safety, tolerability, PK, and preliminary efficacy of ARV-471 as monotherapy in Japanese participants with ER+IHER2- locally advanced or mBC.

One dose level of ARV-471, 200 mg QD which has been determined as the RP3D as monotherapy in the FIH study (Study ARV-471-mBC-1OJ) conducted outside Japan will be investigated. Six participants will receive ARV-471 at 200 mg QD. If none or 1 participant experience DLT during the first cycle (1 Cycle= 28 days), ARV-471, 200 mg QD will be considered tolerable as monotherapy in Japanese participants. If 2 participants experience DLT, the investigator and the sponsor should discuss the safety and tolerability based on the available data, and then under the agreement between the investigator and the sponsor, an additional 3 participants at the same dose level, up to a total of 9 participants, will be enrolled to further investigate the safety and tolerability of ARV-471 as monotherapy in Japanese participants. If no DLT is reported in an additional 3 participants, 200 mg QD will

be considered tolerable in Japanese participants. If DLT is observed in ⩾33% of participants at 200 mg QD, the investigation at the next lower dose level may be explored.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The first cycle DLT is the primary endpoint of this study. The occurrence of DLTs observed in the dosing cohort in Japanese population is used to confirm the tolerability of the RP3D that was determined in Study ARV-471-mBC-101 conducted outside Japan.

3.2. Secondary Endpoint(s)

3.2.1. Adverse Events

AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study drug.

AEs will be graded by the investigator according to the NCI CTCAE version 5.0 and coded using MedDRA.

The focus of AE summaries will be on TEAE. TEAE is an AE occurring on/after the date of first dose and within 30 days of the last dose of study drug.

3.2.2. Laboratory Test Abnormalities

Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.

3.2.3. Pharmacokinetics Endpoint(s)

The following PK parameters will be assessed when applicable after a single dose and after multiple doses (Table 2)

Table 2. ***Definition of Plasma Pharmacokinetic Parameters for ARV-471 and ARV-473***

Parameter	***Day 1 (D1) or Day 15 (D15)***	***Definition***	***Method of Determination***
C_{max}	*D1 & D15*	*Maximum observed plasma concentration*	*Observed directly from data*
T_{max}	*D1 & D15*	*Time to reach* C_{max}	*Observed directly from data as time of first occurrence*
AUC_{last}	*D1 & D15*	*Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration* (C_{last})	*Linear/Log trapezoidal method*

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

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

3.2.4. Efficacy Endpoints

3.2.4.1. Best Overall Response

BOR will be assessed based on RECIST version 1.1.

ORR is defined as the percentage of participants with a BOR of CR and PR.

CBR is defined as the percentage of participants with BOR of CR, PR and SD of 24 weeks duration or longer.

ORR and CBR are summarized separately by confirmed and unconfirmed response.

3.2.4.2. Progression Free Survival

PFS is the time from the first date of the study intervention to the date of the first documentation of progression, or death due to any cause.

PD will be assessed based on RECIST version 1.1.

3.2.4.3. Duration of Response

DOR is defined for participants with confirmed objective response (as defined above in overall response) as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

DOR is summarized separately by confomed and unconfomed response.

3.3. Other Endpoint(s)

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3.4. Baseline Variables

Baseline characteristics will be collected according to Schedule of Activities as specified in the protocol. No baseline variable will be used for as covariates for the prirmuy statistical analysis. Unless othe1wise specified, the baseline value is defined as the value collected at the time closest to, but prior to, staiiing the study dmg administration in the first cycle.

3.5. Safety Endpoints

3.5.1. Vital signs

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

3.5.2. Electrocardiogram

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

3.5.3. Physical Examination

Body weight and ECOG PS will be assessed.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all paiiicipants will be assessed to detennine if pa1iicipants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standai·d operating procedmes.

Population	Description	Applicable Analysis (for additional information refer to section 6
Full Analysis Set(FAS)	*All enrolled participants who have been assigned to treatment. Participants are analyzed according to the treatment they were assigned.*	Baseline characteristics
Safety Analysis Set(SAS)	*All enrolled participants who receive at least 1 dose of study intervention. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses.*	AEs, Laborato1y data
DLT Evaluable Set	*All enrolled participants who receive at least 75% of the planned dose intensity of study treatment and either experienced DLT or do not have major protocol deviations during the DLT observation period.*	First cycle DLTs
PK Concentration Set	*All enrolled participants who are treated and have at least 1 analyte concentration above the lower limit of quantitation.*	PK concentrations
PK Parameter Set	*All enrolled participants treated who do not have protocol deviations influencing PK assessment and have sufficient infonnation to estimate at least 1 of the PK parameters of interest.*	PK parameters
Response Evaluable Set	*All enrolled participants who received at least one dose of study treatment and had adequate baseline disease assessment. Participants who discontinued early or died will be included.*	Antitumor activities (ORR, CBR, PFS and DOR)
PD/Biomarker Analysis Set(s)	*The PD/Biomarker analysis population is defined as all enrolled participants with at least 1 of the PD/Biomarkers evaluated at pre and/or post dose.*	PD/Biomarkers CCI [redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis will include all data up to a clinical cut-off date coITesponding to 6 months (24 weeks) after last patient is treated. The final analysis of the data will be perfo1med after LPLV. Also, additional analyses may be perfo1med for publication or regulato1y repo1iing pm-poses.

5.1. Hypotheses and Decision Rules

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

5.1.1. Decision Rules for Tolerability of ARV-471 at the RP3D

The target DLT rate is 33%. If a proportion of observed DLTs in this study is less than 33%, the tolerability of the RP3D in Japanese population is considered to be confirmed. Confirmation of the tolerability of the RP3D will be performed using the DLT evaluable set.

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

For more details, see Section 4.1 and 9.5 in Study protocol.

5.2. General Methods

The data will be summarized by dose level, defined by the initial dose of the study intervention administered to participants. If there are multiple dose levels, in addition to data presentation by dose level, the overall summary combining all dose levels may also be presented.

5.2.1. Analyses for Binary Endpoints

Binary data will be summarized using number of participants, frequency, percentage, and the 2-sided 95% CI for the percentage as needed. The CI will be based on Wilson's score method.

Binary data in this study include ORR and CBR.

5.2.2. Analyses for Continuous Endpoints

Continuous data will be summarized with the mean, median, minimum, maximum, standard deviation, and 2-sided 95% CI of the mean as needed.

Continuous data in this study include, but not limited to, vital signs, ECG, certain PK parameters and biomarkers.

5.2.3. Analyses for Categorical Endpoints

Categorical data will be summarized by number of participants, frequency, percentage in each category, and 2-sided 95% CI of the percentage as needed. The CI will be based on Wilson's score method.

Categorical data in this study include, but not limited to, BOR, and AEs and laboratory abnormalities graded by NCI CTCAE v5.0, where each grade is considered as a category.

5.2.4. Analyses for Time-to-Event Endpoints

Time-to-event data will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. The CIs for medians and quartiles are based on the Brookmeyer-Crowley method. The CIs for the estimated probability of an event at a particular time point will be derived using the log(-log) transformation with back transformation to the untransformed scale. The estimate of the standard error will be computed using the Greenwood formula.

Time-to-event data in this study include PFS and DOR.

5.3. Methods to Manage Missing Data

5.3.1. Missing Dates

Date of Last Dose of Study Drug

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no EOT eCRF page and no death date, the patient should be considered to be ongoing and use the cutoff date for the analysis as the last dosing date. Note: the study team should confirm that the patient is actively receiving dose at the time of the data cutoff.

- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page, OR a death date available (within the data cutoff date), then impute this date as the last dose date:

    - = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

    - = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < Month of min (EOT date, death date)

    - = min (EOT date, death date), for all other cases.

Date of Start of New Anticancer Therapy

Incomplete dates for start date of new anticancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses. PD date below refers to PD date by investigator assessment. If the imputation results in an end date prior to the imputed start date then the imputed start date should be set to the end date.

- The end date of new anticancer therapy will be included in the imputations for start date of new anticancer therapy. If the end date of new anticancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anticancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anticancer therapy
- For patients who have not discontinued study treatment at the analysis cutoff date, last dose of study treatment is set to the analysis cutoff date in the imputations below.
- If the start date of new anticancer therapy is completely or partially missing then the imputed start date of new anticancer therapy is derived as follows:
  - Start date of new anticancer therapy is completely missing
  - Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]
  - Only year (YYYY) for start of anticancer therapy is available
  - IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy] THEN imputed start date = 31DECYYYY;
  - ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]
  - THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]
  - ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]
  - THEN imputed start date = 01JANYYYY
  - Both Year (YYYY) and Month (MMM) for start of anticancer therapy are available

    IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy], AND

    MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anticancer therapy]

    THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy], AND

MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anticancer therapy]

THEN

imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anticancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anticancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]

THEN

imputed start date = 01 MMM YYYY.

Missing or Partial Death Dates

It is recommended that the database be designed to mandate a complete death date. When the database does not mandate this, if there is a record for death, but the date is missing or is partial, it will be imputed based on the last contact date.

- If the entire date is missing, the death date will be imputed as the day after the date of last contact.

- If the day or both day and month is missing, the death date will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:

- 1st day of the month and year of death, if day of death is missing, OR
- January 1st of the year of death, if both the day and month of death are missing.

Other Missing or Partial Dates

Imputation methods generally apply to partial dates as follows:

- If the day of the month is missing for a start date used in a calculation, the first of the month will be used to replace the missing date.
- If both the day and month are missing, the first day of the year is used.
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

  These rules are used unless the calculations result in negative time durations (e.g., date of resolution cannot be prior to date of onset). In these cases, the resolution and onset dates will be the same and the duration will be set to 1 day.

5.3.2. Safety Analysis

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied based on the Safety Rulebook.

5.3.3. Efficacy Analysis

For tumor assessment that will be used in the binary/categorical efficacy endpoint, every effort will be made to retrieve data in the CRF, however missing data will be left as is, no imputation will be performed. The reasons for missing tumor assessment will be collected

For the time-to-event endpoints, the missing data handling method will be censoring. Censoring rules for time-to-event endpoints are detailed in Section 6.2.4.

5.3.4. Pharmacokinetic Concentrations

5.3.4.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations BLQ will be set to zero irrespective of where they occur within a profile. Individual BLQ results occurring between two quantifiable concentrations may be identified by the pharmacokineticist as anomalous concentrations.

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 LLQ should be presented to allow appropriate interpretation of the data.

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

In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the LLQ.

5.3.4.2. Deviations, Missing Concentrations and Anomalous Values

Participants who experience events that may affect their PK (e.g., incomplete dosing) may be excluded from the PK analysis.

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND or NS,

2. A deviation in sampling time is of sufficient concern (>10% of the nominal time) or a concentration has been flagged anomalous by the pharmacokinetist.

Note that summary statistics will be only presented at a particular time point if ≥3 data are available unless appropriate cautions and rationale are provided in the study report.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other subjects. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

5.3.5. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC. If a PK parameter cannot be derived from a patient's concentration data due to discontinuation of treatment, the parameter will be coded as NS. (Note that NC values will not be generated beyond the day that a subject discontinues.)

In summary tables, statistics will be calculated by setting NC and NS values to missing; and statistics will be presented for a particular treatment with ⩾3 evaluable measurements. For statistical analyses, PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual subject has a known biased estimate of a PK parameter (due for example to dosing error and an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.6. Pharmacodynamic Parameters

Missing data for the pharmacodynamic parameters will be treated as such and no imputed values will be derived.

5.3.7. QTc

For the corrected QT (QTc) analyses, no values will be imputed for missing data.

5.4. Statistical Considerations of COVID-19 Impacted Data

In March 2020, the WHO announced a global pandemic of the virus SARS-CoV-2 and the resulting disease COVID-19. During the conduct of this trial, if any participant's data is impacted by this pandemic, the following considerations will be given in the data analyses:

a. If a participant dropped out of the study during the DLT evaluation due to COVID-19, a replacement participant may be added.

b. Death caused by COVID-19 is still considered as an "event" in the analysis of PFS. If deemed necessary, a sensitivity analysis may be performed where COVID-19 driven death is censored at the death date.

c. If a scheduled tumor radiographic scan is *delayed* out of the Schedule of Activity allowable window, or is *missing* (i.e., participant skipped a scheduled tumor radiographic scan) due to any reasons related to the pandemic, this delay or missingness does not alter the censoring rules for PFS or DOR as described in Section 6.2.4.2 and 6.2.4.3. A censoring reason of "COVID-19" may be added to the PFS or DOR summary if the specific reason of tumor scan delay or missing can be attributed to COVID-19. If deemed necessary, a sensitivity analysis may be performed where participants would be censored on the date of COVID-19 diagnosis.

   In the confirmed ORR or CBR analysis, as described in Section 6.2.4.1, if a response can't be confirmed by a subsequent tumor scan because of the pandemic (i.e., the subsequent tumor scan wasn't performed), then the initial response will be considered as unconfirmed. This is a conservative approach. No sensitivity analysis will be performed.

d. Any COVID-19 related symptoms are to be captured as adverse events in the case report form. Those adverse events will be summarized in the same manner as other adverse events. If a label or phrase of COVID-19 can be identified in the investigator provided adverse event term, then a separate AE listing may be provided for just the COVID-19 related events.

e. If identifiable, the COVID-19 related data points, including missing data where the reason of missing is identified as COVID-19 related (site closure hence data could not captured; participants skipped a visit because of concern over the pandemic), protocol deviations driven by COVID-19, safety events caused by COVID-19 may be separately listed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Dose-Limiting Toxicities

6.1.1.1. Main Analysis

- Analysis set: DLT Evaluable Set.

- Analysis methodology: Whether an adverse event a participant experienced during the DLT window (i.e., first 28 days of Cycle 1) is determined as a DLT or not is based on the DLT definitions provided in Section 4.3.1 of the protocol. A DLT yes/no checkbox will be provided in the CRF, where the investigator provides his/her judgement if an event is a DLT or not. However, the final determination will be reached between the investigators and the sponsor. These final decisions will be documented.

  The DLT events will be summarized by dose level. A listing of the DLTs events will also be provided in which the participant primary diagnosis, dose level the participant was enrolled to, DLT event start day and stop day relative to the cycle 1 day 1 dose date, the DLT event term, NCI CTCAE grade, relatedness to the investigational product (ARV-471), outcome of the event, along with other variables deemed important, will be included.

- Missing data: All enrolled participants should have an indicator variable derived to be either 1 (yes) or 0 (no) based on the DLT definitions and participant's safety data during the DLT observation window. If a participant fails to have a value on the indicator variable because the participant is considered not to be DLT-evaluable, the participant may be replaced.

6.2. Secondary Endpoint(s)

6.2.1. Adverse Events

- Analysis set: Safety Analysis Set.

- Analysis methodology: The number and percentage of participants who experienced any AE, SAE, TRAE, and treatment related SAE will be summarized by SOC and PT according to maximum toxicity grades. Summary tables sorted in decreasing order of frequency will be provided if deemed necessary.

  The summaries will present AEs on the entire study period. Additionally, summaries of AEs leading to death and premature withdrawal from study treatment will be provided.

- Missing data: If AE start or stop date is missing, imputation will be performed according to Section 5.3.1. The imputed dates will be used to determine whether the AE is to be included in the TEAE summary. The missing AE start or stop dates will be listed as is in AE listings. When the CTCAE grade is missing for an AE, the AE will be excluded from the CTCAE grade summary table.

6.2.2. Laboratory Abnormalities

- Analysis set: Safety Analysis Set.

- Analysis methodology: Laboratory tests in this study include several panels; hematology, chemistry, coagulation.

  The frequency and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade (based on NCI CTCAE version 5.0) observed for each laboratory assay. Summaries of laboratory tests results by visit will not be provided unless deemed necessary. Shift tables may be provided for selected laboratory tests.

  The summaries will be presented for the entire on-treatment period.

  Hematology, serology, and coagulation lab results can be combined into one summary output. Separate summaries will be created for chemistry tests. Urinalysis and pregnancy tests will only be presented in data listings.

- Missing data: Intermediate missing values (i.e., values collected between baseline and the last study measurement) will not be imputed.

6.2.3. Pharmacokinetic Analysis

6.2.3.1. PK Concentration Analysis

- Analysis set: PK Concentration Set.

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

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

- Missing data: Missing concentration and BLQ values will be handled according to data will be handled according to Section 5.3.4.

6.2.3.2. PK Parameter Analysis

- Analysis set: PK Parameter Set.

- Analysis methodology: *Plasma PK parameters for ARV-471 and ARV-473 following multiple dose administration will be derived from the concentration-time profiles using noncompartmental methods as data permit. The PK parameters to be assessed in this study, their definition, and method of determination are outlined in* Table 2. *In all cases,*

actual PK sampling times will be used in the derivation of PK parameters. The single-dose PK parameters on Day 1 in Cycle 1 and steady-state PK parameters on Day 15 in Cycle 1 will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and geometric CV) by cycle and day.

For summary statistics of C_{trough} at steady state, within-patient average C_{trough} data calculated using the C_{trough} data obtained from all visits for each patient will be used. *C_{trough} at steady state will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and geometric CV) by cycle and day. C_{trough} at steady state will be plotted by cycle and day, and also plotted using a box whisker plot by cycle and day.*

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

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

- Missing data: Missing parameter data will be handled according to Section 5.3.5.

6.2.4. Efficacy Analysis

6.2.4.1. Best Overall Response

- Analysis sets: Response Evaluable Set.

- Analysis methodology: BOR derivations are described below based on whether or not confirmed responses are required. The BOR will be reported based on investigator assessment.

BOR Based on Confirmed Responses

CR: Two objective statuses of CR a minimum of 4 weeks apart documented before PD.

PR: (applicable only to patients with measurable disease at baseline): Two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of 4 weeks apart documented before PD, but not qualifying as CR. Sequences of PR- Stable-PR are considered PRs as long as the 2 PR responses are observed at a minimum of 4 weeks apart.

SD: (applicable only to patients with measurable disease at baseline): At least 1 objective status of stable disease or better documented at least 8 weeks after first dose date and before PD but not qualifying as CR or PR.

Non-CR/non-PD: (applicable only to patients with non-measurable disease at baseline): At least 1 non-CR/non-PD assessment (or better) documented at least 8 weeks after 'start date' and before first documentation of PD (and not qualifying for CR or PR).

PD: Progression documented within 16 weeks after first dose date and not qualifying as CR, PR or SD.

NE: All other cases. Note that reasons for NE should be summarized

BOR Based on Unconfirmed Responses

uCR: One objective status of CR documented before PD.

uPR: (applicable only to patients with measurable disease at baseline): One objective status of PR documented before PD but not qualifying as uCR.

SD: (applicable only to patients with measurable disease at baseline): At least 1 objective status of stable disease or better documented at least 8 weeks after first dose date and before PD but not qualifying as uCR or uPR

Non-uCR/non-PD: (applicable only to patients with non-measurable disease at baseline): at least 1 non-CR/non-PD assessment (or better) documented at least 8 weeks after first dose date and before first documentation of PD (and not qualifying for uCR or uPR).

PD: Progression documented within 16 weeks after first dose date and not qualifying as uCR, uPR or SD.

NE: All other cases. Note that reasons for NE should be summarized.

Both confirmed ORR and uORR will be determined based on the confirmed and unconfirmed CR and PR. ORR will be based on the BOR of a participant, according to RECIST version 1.1.

Similarly, confirmed CBR and uCBR will be determined based on the BOR on confirmed and unconfirmed response.

ORR/uORR and CBR/uCBR, and their 95% confidence interval as described in Section 5.2.1 will be presented for each dose level and the total across all dose levels (if there are multiple dose level).

Tumor response will be presented in the form of participants data listings that include, but are not limited to; tumor type, actual received day 1 dose, tumor response at each assessment, and best overall response. Progression date, death date, date of first response, last assessment date, and date of last contact will also be listed.

Additionally, a swimmer plot will be provided to display tumor response overtime and a waterfall plot displaying the best percentage change in tumor size will be provided.

- Missing data: Missing tumor data will not be imputed and treated as non-responder in the analyses for ORR and CBR.

6.2.4.2. Progression Free Survival

- Analysis Set: Response Evaluable Set.

- Analysis methodology: PFS will be summarized using the Kaplan-Meier method, as described in Section 5.2.4. PFS may also be displayed graphically when appropriate.

  PD or death within 16 weeks of the last adequate tumor assessment or within 16 weeks after the first dose date will be counted as an event according to the tumor assessment date or date of death, as appropriate.

  Participants without an event or with an event after 2 or more inadequate or missing tumor assessments will be censored on the date of the last adequate tumor assessment that documented no progression; deaths within 16 weeks after first dose date for participants who did not initiate new anticancer therapy will be considered an event. In addition, if a new anticancer therapy is started prior to an event, the participant will be censored on the date of the last adequate tumor assessment that documented no progression prior to the start of the new anticancer therapy.

  An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined. Time points where the response is NE or no assessment was performed will not be used for determining the censoring date.
  Participants with no baseline tumor assessment (including patients with an inadequate baseline assessment) or with no adequate post-baseline tumor assessments within 16 weeks after the first dose date will be censored on the first dose date, unless the participant dies within 16 weeks of the first dose date, in which case, death will be an event on date of death.

  Events and censoring rules are summarized in Table 3.

  Any tumor scan or response data impacted by COVID-19 will be handled according to Section 5.4.

Table 3. PFS Censoring Rules

Situation	Date of Event/Censoring	Outcome
No adequate baseline assessment	First dose date[a]	Censored[a]
PD or death - after at most 1 missing or inadequate post-baseline tumor assessment, or - ≤ 16 weeks after first dose date	Date of PD or death	Event
PD or death - after 2 or more missing or inadequate tumor assessments	Date of last adequate tumor assessment[b] documenting no PD prior to new anticancer therapy or missed tumor assessments	Censored
No PD		
New anticancer therapy given prior to PD or death		

a. If the patient dies ≤ 16 weeks after first dose date and did not initiate new anticancer therapy, the death is an event with date on death date.
b. If there are no adequate post-baseline tumor assessments prior to the PD or death, then the time without adequate assessment should be measured from the first dose date; if the criteria were met, the censoring will be on the first dose date.

- Missing data: For time-to-event endpoints, missing data will be handled by the censoring rules and no imputation will be performed.

6.2.4.3. Duration of Response

- Analysis set: Including only participants with objective response in Response Evaluable Set.

- Analysis methodology: For patients with an objective response, DOR is the time from first documentation of PR or CR to date of first documentation of PD or death due to any cause, whichever occurs first. Both confirmed DOR and uDOR will be determined separately for the subset of participants with a confirmed and unconfirmed objective response of CR or PR.

  DOR will be summarized using the Kaplan-Meier method if the number of participants with objective response will be >2. If the number of participants with objective response will be ≤2, DOR will be summarized using descriptive statistics.

  When using the Kaplan-Meier method, the outcome, event dates and reasons for censoring for DOR will match exactly those for the analysis of PFS based on the primary definition of PFS that will be selected for the trial; however, patients will not be censored for inadequate baseline assessment or for no adequate post-baseline assessment, as only patients with an objective response are included in this analysis of DOR.

- Missing data: Same as handling for analysis of PFS.

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[redacted]

6.4. Subset Analyses

There are no planned subset analyses.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

The Full Analysis Set will be used for analysis of baseline characteristics.

Baseline characteristics will be summarized and/or listed in paiiicipant level data listings:

- Demographics will be summarized by dose level. Demographic data will also be listed in a data listing.
- Primary diagnosis will be listed for all enrolled paiiicipants. The dmation since prima1y diagnosis (months), defined as

  (date of the first dose of study intervention- date of the first diagnosis)/ 30.4375,

  will be summarized by dose level.
- Baseline signs and symptoms will be sUllllnai·ized by dose level. This data will also be listed for all enrolled paiiicipants.
- ECOG perfo1mance status will be sUllllnarized by dose level.

Prior medication, medical histo1y will not be summarized but listed if deemed necessaiy.

6.5.2. Study Conduct and Participant Disposition

An accounting of the study participants will be tabulated. The paiiicipant dose level coho1i will be listed. The Full Analysis Set will be used.

Paiiicipant discontinuation from treatment and study will be tabulated and listed for each paiiicipant with their reason for discontinuation. The Safety Analysis Set will be used.

6.5.3. Study Treatment Exposure

The Safety Analysis Set will be used for the analysis of treatment exposure.

Treatment exposure will be assessed with the following approaches:

- Duration of exposure: Duration of exposure is defined as

  (the last active dose date – the first active dose date + 1) / 7 (weeks).

  Duration of exposure will be summarized, as a continuous variable, by dose level. The number of cycles will also be summarized (≥ 1 cycle; ≥ 2 cycles; ≥ 3 cycles etc.). Frequency and percentage of participants for each cycle may be descriptively summarized by dose level.

- Treatment Compliance: Treatment compliance is defined as

  100 × ([the cumulative actually taken dose] / [the cumulative planned dose]) (%)

  for cycle 1 (for the purpose of defining the population for the DLT evaluation) and over the entire treatment period.

- RDI: RDI is defined as following;

  - By cycle RDI (%) = 100 × [by cycle actual DI]/[intended DI]
  - Overall RDI (%) = 100 × [overall actual DI]/[intended DI]

  Note that the actual intended DI is defined as

  - By cycle actual DI (mg/4-week cycle) = [cumulative dose in the cycle (mg)] / [cycle duration (weeks)/4]
  - Overall actual DI (mg/4-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment (weeks)/4].

  and the intended DI is defined as

  [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] (mg/4-weeks cycle).

Listing by participant level of dosing administration data: cycle number, start date and stop date of dosing period within each cycle (including records with 0 mg), total daily dose received for each dosing period, any missed doses with unknown dates (yes/no), number of missed doses with unknown dates, reason for any dosing changes, total planned dose, total actual dose received, percentage of planned dose, dose reduction (yes/no), and dose interruption (yes/no). The reasons for dose interruption/reduction (e.g., AE), if available, will be also included in the listing.

6.5.4. Other Safety Analyses

The Safety Analysis Set will be used for other safety analyses.

6.5.4.1. Vital Signs

The vital signs will be generally considered as continuous endpoints. Summaries for absolute values, change from baseline and percent change from baseline for the vital signs may be provided if deemed necessary. Also, vital signs during the on-treatment period will be summarized by the categories of abnormality as specified in Table 6. Shift tables will not be provided unless deemed necessary.

Intermediate missing values (i.e., values collected between baseline and the last study measurement) will not be imputed.

6.5.4.2. Electrocardiograms

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

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

Table 4. ***Safety QTcF Assessment***

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

Also, PR and QRS will be summarized by the categories of abnormality as specified in Table 5.

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point for summarization and categorical analysis. If any of the 3 individual ECG tracings at each time point has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 ms value in appropriate clinical context. Changes from baseline will be defined as the change between the post-dose QTcF value and the average of the time-matched baseline triplicate values on Day 1, or the average of the pre-dose triplicate values on Day 1.

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

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

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

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

Intermediate missing values (i.e., values collected between baseline and the last study measurement) will not be imputed.

6.5.4.3. Physical Examination

Physical examination generally will not be summarized or listed except vital signs or ECG. Any change from baseline considered by the investigation to be clinically significant should be recorded as an AE in the CRF, thus will be analyzed in the adverse events data.

7. INTERIM ANALYSES

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

APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs

Table 5. Clinically Relevant Categories for Pulse Rate and QRS

Pulse Rate (msec)	min. <50	max. >120
Pulse Rate (msec) increase from baseline	Baseline ≥200 and max. ≥25% increase	Baseline <200 and max. ≥50% increase
QRS (msec)	max. ≥200	
QRS (msec) increase from baseline	Baseline ≥100 and max. ≥25% increase	Baseline <100 and max. ≥50% increase

Table 6. Clinically Relevant Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	≥160 max.
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	≥100 max.
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfil these criteria are to be listed in the study report.

Appendix 2. List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC	area under the plasma-concentration curve
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the plasma concentration-time curve from time zero to time tau
BID	twice daily
BLQ	below the limit of quantification

Abbreviation	Term
BOR	best overall response
BP	blood pressure
CBR	clinical benefit response
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum observed plasma concentration
C_{min}	lowest concentration observed during the dosing interval
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
C_{trough}	pre-dose plasma concentration during multiple dosing
CV	coefficient of variation
DI	dose intensity
DLT	dose-limiting toxicity
CCI	[redacted]
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
ER	estrogen receptor
CCI	[redacted]
FIH	first-in-human
HER2	human epidermal growth factor receptor 2
HR	heart rate
LLQ	lower limit of quantification
LPLV	last participant last visit
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
$MRAUC_{tau}$	ARV-473 to ARV-471 ratio for AUC_{tau}
MRC_{max}	ARV-473 to ARV-471 ratio for C_{max}
MTD	maximum tolerated dose
NA	not applicable
NC	not calculated
NCI	National Cancer Institute
ND	not done
NE	Non-evaluable
NS	no sample
ORR	objective response rate
OS	overall survival

Abbreviation	Term
PD	pharmacodynamic(s) or progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PT	preferred term
QD	once daily
QRS	time from the beginning of the Q wave to the end of the S wave in the electrocardiogram
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
R_{ac}	accumulation ratio based on AUC (observed)
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP3D	recommended phase 3 dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
$t_{½}$	terminal elimination half-life
$t_{½eff}$	effective half-life based on accumulation ratio
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum concentration
TRAE	treatment-related adverse event
uCR	unconfirmed complete response
uCBR	unconfirmed clinical benefit response
uPR	unconfirmed partial response
uORR	unconfirmed overall response
V_z/F	apparent volume of distribution
WHO	World Health Organization