Protocol *C4891029*

An Interventional, Phase 1, Open-Label, Fixed-Sequence, 2-Period Study to Evaluate the Effect of A Single Oral Dose of ARV-471 (PF-07850327) on the Pharmacokinetics of Rosuvastatin in Healthy Participants

Statistical Analysis Plan
(SAP)

Version: 1

Date: 23 Jan 2023

[redacted]

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NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 23 Jan 2023	Original 04 Nov 2022	N/A	N/A

2. INTRODUCTION

ARV-471 (PF-07850327) is a potent, selective, orally bioavailable PROTAC® small molecule that induces degradation of the ER. ARV-471 is a hetero-bifunctional PROTAC® molecule that simultaneously binds the ER and the cereblon E3 ligase complex, enabling protein-protein interactions between ER and the ligase complex. As a result, the ER becomes poly-ubiquitinated on accessible lysine residues and subsequently undergoes targeted degradation by the proteasome.

Rosuvastatin is a prototypical substrate of BCRP. Administration of rosuvastatin with ARV-471 may lead to increased systemic exposure of rosuvastatin. The objective of this study is to estimate the effect of ARV-471 on the PK of rosuvastatin in healthy participants.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4891029.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives, Endpoints, and Estimands

The following are the objectives and endpoints in this study. Estimand framework will not be applied to this Phase 1 study in healthy participants.

Objectives	*Endpoints*
Primary:	***Primary:***
• *To estimate the effect of a single oral 200 mg dose of ARV-471 on a single dose PK of rosuvastatin in healthy participants.*	• *Plasma rosuvastatin C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated)*
Secondary:	***Secondary:***
• *To evaluate the safety and tolerability of rosuvastatin alone and following co-administration with a single oral dose of ARV-471.*	• *TEAEs, clinical laboratory tests, vital signs, PE, and ECGs*
Other:	***Other:***
• *To characterize the* CCI *of ARV-471 and its epimer, ARV-473 after a single oral 200 mg dose of ARV-471.*	• CCI *as data permit and as appropriate* • *Rosuvastatin PK parameters: plasma C_{last}, AUC_{last}, T_{max}, T_{last}, $t_{1/2}$, CL/F, V_z/F, as data permit*

2.3. Study Design

This will be a Phase 1, open-label, 2-period, fixed-sequence study, estimating the effect of a single oral dose of ARV-471 on the PK of a BCRP substrate, rosuvastatin, in healthy male participants and healthy female participants of non-childbearing potential. An attempt will be made to enroll more than 50% participants as female participants with non-childbearing potential in this study since ARV-471 is being developed for the treatment of mBC.

This study will consistent of 2 Periods. In Period 1, a standard breakfast will be provided approximately 2 hours (120 minutes) prior to rosuvastatin single dose (10 mg) administration on Day 1. The breakfast will be required to be completely consumed within an approximately 20-minute period. To avoid rosuvastatin effects from the previous period, a minimum washout period of 5 days will be required after rosuvastatin administration on Period 1 Day 1.

In Period 2, a standard breakfast will be provided approximately 30 minutes prior to ARV-471 single dose (200 mg) on Day 1. The breakfast will be required to be completely consumed within an approximately 20-minute period. A single dose of 10 mg rosuvastatin will be administered approximately 1.5 hour (90 minutes) after ARV-471 dosing, which will be approximately 2 hours (120 minutes) after the start of the breakfast. Serial PK samples

will be collected up to 72 hours following administration of rosuvastatin in each period to estimate the single dose PK parameters of rosuvastatin.

A sufficient number of participants will be screened to ensure that at least 12 participants will be enrolled in the study. Participants who withdraw may be replaced at the discretion of the sponsor.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints of the study are plasma C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated) of rosuvastatin alone and following co-administration with a single oral 200 mg dose of ARV-471. Adjusted geometric mean ratios of AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} will be derived.

The plasma PK parameters of rosuvastatin will be derived from the concentration-time profiles as detailed in Table 2 for each period *if applicable. Actual PK sampling times will be used in derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.*

Table 2. PK Parameters

Parameter[a]	**Analyte**	***Definition***	***Method of Determination***
AUC_{last}	rosuvastatin, CCI [redacted]	*Area under the concentration-time profile from time 0 to the time of last quantifiable concentration (C_{last}).*	*Linear/Log trapezoidal method.*
AUC_{inf}[a]	rosuvastatin, CCI [redacted]	*Area under the concentration-time profile from time 0 extrapolated to infinite time.*	*AUC_{last} + (C_{last}*/k_{el}), Where C_{last}* is the predicted concentration at the last quantifiable time point estimated from the log-linear regression analysis and k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.*
C_{max}	rosuvastatin, CCI [redacted]	*Maximum concentration*	*Observed directly from data.*
C_{last}	rosuvastatin, CCI [redacted]	*Last measurable observed concentration*	*Observed directly from data.*
T_{max}	rosuvastatin, CCI [redacted]	*Time for C_{max}*	*Observed directly from data.*
T_{last}	rosuvastatin, CCI [redacted]	*Time for C_{last}*	*Last measurable observed concentration*
$t_{½}$[a]	rosuvastatin, CCI [redacted]	*Terminal elimination half-life*	*$Log_e(2)/k_{el}$,. Only those data points judged to describe the terminal log-linear decline will be used in the regression.*
CL/F[a]	rosuvastatin, CCI [redacted]	*Apparent clearance*	*Dose/(AUC_{inf})*
V_z/F[a]	rosuvastatin, CCI [redacted]	*Apparent volume of distribution*	*Dose/(AUC_{inf} *k_{el})*
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

a. if data permits and as appropriate.

3.2. Secondary Endpoints

The secondary endpoints are the overall safety profile of rosuvastatin alone and following co-administration with a single oral 200 mg dose of ARV-471, as characterized by adverse events, laboratory tests, vital signs, and ECGs (discussed in Section 3.5).

3.3. Other Endpoints

CCI for ARV-471 and ARV-473 will be derived (as data permit and as appropriate) from the concentration time profiles as detailed in Table 2 for each analyte if applicable. *Actual* CCI *times will be used in derivation of* CCI*. In the case that actual* CCI *times are not available, nominal* CCI *time will be used in the derivation of* CCI.

In addition, CCI rosuvastatin PK parameters (C_{last}, AUC_{last}, T_{max}, T_{last}, $t_{1/2}$, CL/F, V_z/F, as data permit) will also be derived following the methodology described above.

3.4. Baseline Variables

Baseline participant characteristics will be collected according to the schedule of activities (SoA) as specified in the protocol.

3.5. Safety Endpoints

The following data will be considered in standard safety summaries (see protocol for collection days, baseline assessment, and list of parameters):

- Adverse events (AE)
- Laboratory data
- Vital signs data
- ECG results

3.5.1. Adverse Events

Any adverse event occurring following start of treatment will be considered a treatment emergent adverse event (TEAE). Events that occur during follow-up within the lag time of up to 28 days after the last dose of study intervention will be counted as treatment emergent and attributed to the last treatment taken. Events that occur during the washout period between study periods will be counted as treatment emergent and attributed to the previous treatment taken. The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. To determine if there are any clinically significant laboratory abnormalities, haematological, clinical chemistry

(serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

For both Periods, the baseline measurement is the predose measurement on Period 1 Day -1. Changes from baseline will be defined as the change between the baseline and postdose measurements.

3.5.3. Vital Signs

Supine blood pressure (BP) and pulse rate (PR) will be measured at times specified in the SoA in the protocol.

For both Periods, the baseline measurement is the predose measurement on Period 1 Day 1. Changes from baseline will be defined as the change between the baseline and postdose measurements.

3.5.4. Electrocardiograms

QT interval, QTcF, PR, QRS and heart rate (HR) will be recorded at each assessment time indicated in the SoA given in the protocol. If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{(1/3)} \text{ where } RR = 60/HR \text{ (if not provided)}$$

For both Periods, the baseline value is the average of the triplicate ECG measurements collected before dose administration on Period 1 Day 1. Changes from baseline will be defined as the change between the baseline ECG and the postdose ECG measurement.

The maximum absolute value (postdose) and the maximum increase from baseline for QTcF over all measurements taken postdose will be determined.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each postdose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database. Classifications will be documented per standard operating procedures.

Participant Analysis Set	***Description***
Enrolled	*"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and*

Participant Analysis Set	***Description***
	assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety Analysis Set	*All participants enrolled and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.*
PK Concentration Set	*All participants who are in the Safety Analysis Set and have at least 1 rosuvastatin concentration measured.*
PK Parameter Set	*All participants who are in the Safety Analysis Set and have at least 1 PK parameter of interest (C_{max} or AUC of rosuvastatin).*

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analysis will be performed after study participant data set release following last participant last visit.

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

5.2.1. Analyses for Binary/Categorical Endpoints

For binary or categorical variables, number of participants, numbers and percentages of participants meeting the categorical criteria will be presented in accordance with the Clinical Data Interchange Standards Consortium and Pfizer Standards (CaPS).

5.2.2. Analyses for Continuous Endpoints

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum in accordance with the CaPS. For appropriate PK parameters, geometric mean and geometric coefficient of variation (%CV) will also be summarized.

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic Data

Methods to handle missing PK data are described below.

Concentrations Below the Limit of Quantification:

In all data presentations except listings, concentrations below the limit of quantification (BLQ) will be set to zero. In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

Deviations, Missing Concentrations and Anomalous Values:

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

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample).

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the pharmacokineticist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

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 participants. 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 or pharmacokineticist.

PK Parameters:

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (not calculated; NC values will not be generated beyond the day that a participant discontinues). In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular treatment with ≥3 evaluable measurements. PK parameter analyses will not be performed for a particular parameter if more than 50% of the data are NC.

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

5.3.2. Safety Data

Missing values in standard summaries of AEs, laboratory data, vital signs, and ECGs will be imputed according to CaPS.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

The primary endpoints plasma C_{max}, AUC_{inf} (if data permit, otherwise AUC_{last}) of rosuvastatin alone and following co-administration with a single 200 mg dose of ARV-471 will be summarized descriptively by treatment and will include the set of summary statistics as specified in Table 3. *For comparison of rosuvastatin AUC_{inf}* (if data permit, otherwise AUC_{last}) *and C_{max} with and without ARV-471, box and whisker plots of these parameters will be plotted by period.*

Natural log transformed parameters (AUC_{inf} [if data permit)], AUC_{last}, and C_{max}) of rosuvastatin will be analyzed using a mixed effect model with treatment as fixed effects and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted 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. Rosuvastatin administered alone will be the reference treatment and ARV-471 co-administered with rosuvastatin will be the test treatment.

Residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the CSR. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be provided in the clinical study report.

6.2. Secondary Endpoints

Safety data will be analyzed in accordance with the CaPS (see Section 6.6).

6.3. Other Endpoints

CCI [redacted] and other rosuvastatin PK parameters, will be summarized descriptively in accordance with Pfizer data standards for the PK Parameter Set, as data permit and as appropriate, and will include the set of summary statistics as specified in Table 3. Missing values will be handled as detailed in Section 5.3.1.

Table 3. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, C_{max}, CL/F, V_z/F, C_{last}, CCI [redacted]	N, arithmetic mean, median, SD, %CV, minimum, maximum, geometric mean and geometric %CV
T_{max}, T_{last}	N, median, minimum, maximum
$t_{½}$	N, arithmetic mean, median, SD, %CV, minimum, maximum

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by analyte and treatment: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the clinical study report.

PK concentration summaries:

The plasma concentrations of each analyte will be listed and descriptively summarized by nominal PK sampling time and treatment for the PK Concentration Set. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Mean and median plasma concentration profiles will be presented on both linear and semi-log scales.

Presentations for plasma concentrations for each analyte will include:

- A listing of all concentrations sorted by participant ID, period, treatment and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be provided in a separate listing.

- A summary of concentrations by treatment and nominal time postdose, where the set of statistics will include n, mean, median, SD, %CV, minimum, maximum and the number of concentrations above the LLQ.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each treatment per scale).

- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all treatments) per scale].

6.4. Subset Analyses

There are no planned subset analyses.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Demographic Summaries

Demographic characteristics will be summarized for enrolled population in accordance with the CaPS.

6.5.2. Study Conduct and Participant Disposition

Participants evaluation groups will show end of study participant disposition and will show which participants were analyzed for pharmacokinetics, as well as for safety. Frequency counts will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the CaPS.

6.5.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.5.4. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported in the listings.

6.6. Safety Summaries and Analyses

All safety analyses will be performed on the Safety Analysis Set.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

6.6.1. Adverse Events

Adverse events will be reported in accordance with the CaPS.

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with the CaPS.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the CaPS.

6.6.3. Vital Signs

Vital signs data will be listed and summarized by treatment in accordance with the CaPS.

6.6.4. Electrocardiograms

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

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

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*

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 modeling, and/or supporting clinical development.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Available safety and PK data may be reviewed.

APPENDICES

Appendix 1. SAS Code for Analyses

An example of the PROC MIXED code is provided below:

For the primary objective:

- **Treatment B (Test) vs Treatment A (Reference)**

```
proc mixed data=tab.pk;
        class trt participant;
        model l&var=trt / ddfm=KR;
        random participant / subject=participant;
        lsmeans trt;
        estimate 'B vs A' trt  -1  1  /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows
A: single dose of rosuvastatin 10 mg
B: single dose of 200 mg ARV-471 + single dose of rosuvastatin 10 mg
*/
```

Appendix 2. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AE	adverse event
ANOVA	analysis of variance
$AUC_{extrap\%}$	the percent of AUC_{inf} based on extrapolation
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
BCRP	breast cancer resistance protein
BLQ	below the limit of quantification
BP	blood pressure
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CI	confidence interval
CL/F	apparent clearance after oral dose
C_{last}	last quantifiable concentration
C_{max}	maximum observed concentration
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
ER	estrogen receptor
HR	heart rate
k_{el}	elimination rate constant estimated from the log-linear regression analysis
LLQ	lower limit of quantification
mBC	metastatic breast cancer
ms	milliseconds
CCI [redacted]	[redacted]
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PK	pharmacokinetic(s)
PR	pulse rate
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
r^2	goodness of fit statistic from the log-linear regression

Abbreviation	Term
RR	respiratory rate
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
$t_{1/2}$	terminal elimination half-life
TEAE	treatment emergent adverse event
T_{last}	time for C_{last}
T_{max}	time for C_{max}
V_z/F	apparent volume of distribution after oral dose