CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: 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

Study Number: C4891016

Regulatory Agency or Public Disclosure Identifier Number: NCT05463952

Study Phase: 1

Name of Study Intervention: PF-07850327/ ARV-471/ Vepdegestrant

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR Version 1.0 and 06 September 2023

Number of Study Center(s) and Investigator(s):

A total of 6 participants were enrolled at 2 centers in Japan.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Not Applicable.

Study Period:

The study initiation date (First participant first visit) was 16 August 2022, and the study primary completion date was 04 May 2023.

This study was neither discontinued nor interrupted.

Rationale:

The purpose of this study is to confirm safety and tolerability at the recommended phase 3 dose (RP3D) of ARV-471 in Japanese participants with estrogen receptor positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) locally advanced or metastatic breast cancer (mBC).

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Objectives, Endpoints, and Statistical Methods:

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of ARV-471 at the RP3D	First cycle DLTs
Secondary	
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
To characterize the single-dose and multiple-dose PK of ARV-471 and ARV-473 (an epimer of ARV-471)	• The following PK parameters were 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*, $R_{ac,}$ $t_{½}$, $t_{½\,eff}$, MRC_{max}, and $MRAUC_{tau}$ • *ARV-471 only $t_{½}$ for single dose and multiple doses and V_z/F for multiple doses were calculated only if data permitted
To explore preliminary antitumor activity	Antitumor activity of ARV-471 was 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 • Time to event endpoints: PFS, DOR

AE = adverse event; AUC_{tau} = area under the plasma concentration-time curve from time zero to time tau; AUC_{last} = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; CBR = clinical benefit response; CL/F = apparent clearance; C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration; C_{trough} = pre-dose plasma concentration during multiple dosing; CTCAE = common terminology criteria for adverse event; DLT = dose limiting toxicity; DOR = duration of response; $MRAUC_{tau}$ = metabolite ratio for AUC_{tau}; MRC_{max} = metabolic ratio for C_{max}; ORR = objective response rate; PFS = progression free survival; SD = stable disease; $t_{½}$ = terminal elimination half-life; $t_{½\,eff}$ = effective half-life based on accumulation ratio; T_{max} = time to reach maximum concentration; V_z/F = apparent volume of distribution; R_{ac} = accumulation ratio based on AUC (observed).

Methodology:

This was a single country, non-randomized, open-label, Phase 1 study to evaluate the safety, tolerability, PK, and preliminary efficacy of ARV-471 as monotherapy in Japanese participants with ER+/HER2- locally advanced or mBC. In the event of dose limiting toxicity (DLT) in ≥33% of participants at 200 mg once daily (QD), the investigation at the next lower dose level was potentially to be explored.

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Number of Participants (planned and analyzed):

Six participants were to be enrolled in this study to evaluate DLT, and the RP3D (200 mg QD) which was determined in Study ARV-471-mBC-101 was to be administered to each participant. An additional 3 participants were to be enrolled depending on the number of participants with DLTs (total up to 9 participants).

A total of 6 participants were screened for entry into the study and all screened participants received at least 1 study intervention and were included in the Full Analysis Set, Safety Analysis Set, and DLT Evaluable Set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants ≥20 years at the time of the Screening visit with ER+/HER2- Locally Advanced or Metastatic Breast Cancer (mBC), willing and able to give signed informed consent and met all inclusion criteria and no exclusion criteria were enrolled in the study.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Table 1. Study Intervention(s) Administered

Intervention Name	ARV-471
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	100 mg
Dosage Level(s)	200 mg
Route of Administration	Oral
Use	Experimental
IMP or NIMP	IMP
Vendor Lot no.	20AR8804.HQ00001
Pfizer Lot no.	22-DP01141
Sourcing	Provided centrally by the sponsor. Refer to the product specific IP manual.
Packaging and Labeling	Study intervention was provided in a high-density polyethylene bottle with child-resistant cap. Each bottle was labeled as required per country requirement
Investigational Product Description	PF-07850327 (ARV-471) 100 mg Oval Convex Blue Film Coated Tablet 20% DL
Current/Former Name(s) or Alias(es)	NA

Source: Appendix 16.1.6

Duration of Study Intervention:

Treatment with study intervention was continued until either disease progression, withdrawal from treatment, or unacceptable toxicity, whichever occurred first.

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Summary of Results:

Demographic and Other Baseline Characteristics:

All 6 participants (100.0%) were Japanese females and between 45 – 64 years of age. Five participants (83.3%) received ≥3 regimens of prior cancer treatments for advanced disease. In addition, 5 participants (83.3%) received prior CDK4/6 inhibitors.

Exposure:

The median duration of treatment was 9.8 weeks (range: 6.0 to 28.0 weeks). All participants (100.0%) received at least 2 cycles of treatment, and 2 participants (33.3%) received ≥6 cycles of treatment and were ongoing treatment at the time of data cutoff for this CSR.

Efficacy Results:

Among the 6 evaluable participants, the confirmed best overall response as assessed by investigator using RECIST version 1.1 was stable disease (SD) for 2 participants (33.3%) and progressive disease (PD) for 4 participants (66.7%). Two participants were on treatment at the time of data cut-off (24.1 and 28.4 weeks after the first dose, respectively) and continued SD at Week 24 assessment. No participants achieved ORR. The median of progression free survival (PFS) was 2 months (95% CI: 1.4, not evaluable [NE]).

Safety Results:

Overall, 4 participants (66.7%) in the study experienced at least 1 all-causality treatment emergent adverse event (TEAE). All reported TEAEs were of Grade 1 or 2. No participant reported TEAE of Grade 3, 4, and 5 intensities. All hematology and chemistry laboratory parameters were Grade 2 or less of severity. None of the participants experienced a serious adverse event (SAE).

No TEAEs associated with permanent discontinuations were reported, no participants reported or TEAEs leading to dose reduction.

No participants in the DLT Analysis Set reported DLTs.

Pharmacokinetic Results:

Time to reach ARV-471 peak plasma concentrations were similar after a single dose and multiple daily doses of 200 mg with median T_{max} of 4.74 hours and 4.69 hours, respectively. Exposure following single dose on Day 1, as measured by geometric mean AUC_{tau} and C_{max} were 10400 ng•hr/mL and 630.9 ng/mL, respectively. Geometric mean AUC_{tau} and C_{max} following multiple daily dosing on Day 15, were 18310 ng•hr/mL and 1056 ng/mL, respectively, resulting in an accumulation ratio of AUC_{tau} (R_{ac}) of 1.760 and corresponding arithmetic mean effective $t_{½}$ ($t_{½\ eff}$) was 20.23 hours. ARV-471 appeared to reach steady state by Cycle 1, Day 8 which is consistent with the $t_{½\ eff}$ value. The geometric mean apparent CL/F was 10.92 L/hr after multiple daily doses. Arithmetic mean C_{trough} value for each patient was calculated using C_{trough} data at Days 8, 15, and 22 of Cycle 1 and Days 1 and 15

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of Cycle 2 and 3, and End of Treatment Visit. Within-participant geometric mean C_{trough} which was calculated using arithmetic mean C_{trough} value for each participant was 583.4 ng/mL (Table 14.4.4.1).

ARV-473, an epimer of ARV-471, was formed and its C_{max} were reached with a median T_{max} of 23.5 hours after a single dose of 200 mg ARV-471. ARV-473 exposures following single dose of ARV-471 on Day 1, as measured by geometric mean AUC_{tau} and C_{max} were 1289 ng•hr/mL and 74.08 ng/mL, respectively. Geometric mean ARV-473 AUC_{tau} and C_{max} following multiple daily ARV-471 dosing on Day 15, were 6175 ng•hr/mL and 292.5 ng/mL, respectively, resulting in an accumulation ratio of AUC_{tau} (R_{ac}) of 4.790 and corresponding arithmetic mean $t_{½\,eff}$ was 71.60 hours. Within-participant geometric mean C_{trough} was 262.9 ng/mL (Table 14.4.4.1). Metabolite to parent ratios for AUC_{tau} and C_{max} were 0.3374 and 0.2770, respectively.

Plasma exposure of ARV-471 and ARV-473 was higher in one of 6 patients which could not be explained.

Pharmacodynamic Results:

The results of exploratory biomarkers and pharmacodynamics analysis is not included in this CSR and will be reported separately.

Other Results: (if applicable):

Not Applicable.

Conclusions:

- No DLTs were reported.
- All reported TEAEs were Grade 1 or 2.
- No participants discontinued the study treatment or required dose reduction due to TEAEs.
- The study demonstrated that ARV-471 at the RP3D (200 mg QD) was tolerable and manageable in Japanese participants.
- ARV-471 median T_{max} were similar after a single dose (4.74 hours) and multiple daily doses (4.69 hours) of 200 mg ARV-471 in Japanese patients. The geometric mean CL/F was 10.92 L/hr after multiple daily doses. Within-participant geometric mean C_{trough} was 583.4 ng/mL. R_{ac} was 1.760 which was observed on Day 15 following multiple daily dosing and corresponding arithmetic mean $t_{½\,eff}$ was 20.23 hours. ARV-471 appeared to reach steady state by Cycle 1, Day 8 which is consistent with the $t_{½\,eff}$ value. ARV-473 median T_{max} after a single dose and multiple daily doses of 200 mg ARV-471 were 23.5 hours and 6.83 hours, respectively in Japanese participants. Within- participant geometric mean C_{trough} was 262.9 ng/mL. R_{ac} was 4.790 which was observed on Day 15 following multiple daily dosing of ARV-471 and corresponding arithmetic mean $t_{½\,eff}$

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was 71.60 hours. Metabolite to parent ratios for AUC_{tau} and C_{max} were 0.3374 and 0.2770, respectively.

- Preliminary efficacy result is limited in interpretation due to small sample size and short duration of follow-up.
- No participant achieved ORR as of the data cutoff for the CSR.
- Two participants (33.3%) were SD and ongoing treatment at time of data cutoff and 4 (66.7%) were PD as best overall response.
- The median PFS was 2.0 months (95% CI: 1.4 months to NE) and there were no deaths in the study.