CLINICAL STUDY REPORT SYNOPSIS

Study Title:	A Phase 1, Open-Label, 2-Period Study to Evaluate the Effect of Multiple Doses of Esomeprazole on the Pharmacokinetics of Single Dose Vepdegestrant (ARV-471, PF-07850327) Under the Fed Condition in Healthy Adult Males and Healthy Adult Females of Nonchildbearing Potential
Study Number:	C4891035
Study Phase:	1
Regulatory Agency or Public Disclosure Identifier Number:	**NCT #:** NCT06275841
Pediatric Investigational Plan Number:	Not Applicable
Study Intervention:	Vepdegestrant (ARV-471)
Indication:	Breast cancer
Study Sponsor:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Study Initiation Date (FPFV):	23 February 2024
Study Completion (LPLV) Date:	24 May 2024
Early Termination Status	This study was not terminated early and was completed as per protocol.
CSR Version and Report Date:	**Document Version** / **Report Date**: Final LPLV CSR Version 1.0 / 12 September 2024

GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country of conduct, including the archiving of essential documents.

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

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

Publications:

None

Brief Description of The Trial Design and Methodology:

Vepdegestrant (also known as ARV-471, PF-07850327) is a potent, selective, orally bioavailable PROTAC® small molecule that induces degradation of the estrogen receptor (ER). Vepdegestrant is currently being developed for the treatment of patients with ER+/HER2- breast cancer (BC).

This was a Phase 1, open-label, 2-period, crossover single-dose study in healthy adult participants. This study will consist of 2 treatments:

- Treatment A: Single vepdegestrant 200 mg dose [redacted], under fed conditions (following an overnight fast of at least 10 hours).
- Treatment B: Esomeprazole 40 mg once a day (QD) dosing from Day 1 to Day 5 and single vepdegestrant 200 mg dose [redacted] on Day 5, under fed conditions (following an overnight fast of at least 10 hours).

A minimum of [redacted] washout period between successive single doses of vepdegestrant is included to minimize any residual vepdegestrant concentrations prior to start of the next treatment period.

The purpose of the study was to investigate the effect of multiple doses of a proton-pump inhibitor (PPI) esomeprazole on the pharmacokinetics (PK) of vepdegestrant under fed conditions in healthy adult participants.

Number of Participants (planned and analyzed):

A total of approximately 12 participants were planned to be enrolled in the study.

A total of 12 participants were enrolled into the study. All enrolled participants were treated and included in the safety analysis. All participants who were treated with at least 1 dose of vepdegestrant and had at least 1 measurable vepdegestrant or [redacted] concentration were included in the PK analysis.

Table S1. Number of Participants (Planned and Analyzed)

Population	N	Definition
Planned	12	The number of participants planned to be enrolled.
Enrolled	12	A participant's or their legally authorized representative's agreement to participant in a clinical study following completion of

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Table S1. Number of Participants (Planned and Analyzed)

		the informed consent process and assignment to study intervention.
Safety analysis set	12	All participants enrolled and who take at least 1 dose of study Intervention.
PK Concentration Analysis Set	12	All participants who are in the Safety Analysis Set and have at least 1 measurable vepdegestrant or [redacted] concentration.
PK Parameter Analysis Set	12	All participants who are in the Safety Analysis Set and have at least 1 of the vepdegestrant or [redacted] PK parameters of primary interest.

PK = pharmacokinetics

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were healthy adult participants, including male participants, and female participants of non-childbearing potential.

Study Intervention:

Enrolled participants received treatments according to the treatment schedule shown in Table S2. A minimum of [redacted] washout period between successive single doses of vepdegestrant was included to minimize any residual vepdegestrant concentrations prior to start of the next treatment period.

For each treatment, after an overnight fast of at least 10 hours and after the collection of the predose vepdegestrant PK sample on Period 1 Day 1 and Period 2 Day 5, participants received the recommended moderate-fat meal (approximately [redacted] calories with a fat content of approximately [redacted]) approximately 30 minutes prior to dosing. The breakfast was completely consumed prior to administration of vepdegestrant. Vepdegestrant was administered as intact tablets with approximately 240 mL of ambient temperature water. Tablets were swallowed whole and not chewed.

Table S2. Treatment Schedule

Sequence	Period 1*	Period 2*
1 (n=12)	A	B

* At least [redacted] between vepdegestrant doses.
Treatment A: Single vepdegestrant 200 mg dose using the [redacted], under fed conditions (following an overnight fast of at least 10 hours).
Treatment B: Esomeprazole 40 mg once a day dosing from Day 1 to Day 5 and single vepdegestrant 200 mg dose [redacted] of the 100 mg strength tablet on Day 5, fed condition.

The manufacturing lot numbers for the study intervention(s) dispensed in this study are provided in Table S3.

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Table S3. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/ Potency	Dosage Form
PF-07850327 (ARV-471) [redacted]	20AR8805.HQ00010	23-DP-01842	[redacted]	Tablet
Nexium (esomeprazole magnesium) Delayed Release Oral Capsules	TL0293	Not applicable	40 mg	Capsule

Global Substantial Modifications

Not applicable

Global Interruptions and re-starts

Not applicable

Endpoints And Statistical Methods:

Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary	**Primary:**				
• To estimate the effect of multiple doses of esomeprazole on the PK of a single oral 200 mg dose of vepdegestrant under fed conditions.	• Plasma vepdegestrant C_{max} and AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated).	• Primary PK analysis	• PK concentration analysis set • PK parameter analysis set	• Observed and imputed data	• Descriptive statistics • Mixed effect model
Secondary	**Secondary:**				
• To evaluate the safety and	• Safety laboratory tests, physical	• Key secondary	• Safety analysis set	• Observed data	• Descriptive statistics

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Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
tolerability of a single oral 200 mg dose of vepdegestrant administered to healthy participants in the absence and presence of multiple doses of esomeprazole.	examination, vital signs, electrocardiograms and adverse event monitoring.	safety analysis			

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; C_{max} = maximum plasma concentration

SUMMARY OF RESULTS:

Participant Disposition

A total of 12 participants were enrolled into the study. All enrolled participants were treated and completed the study.

Demographic and Other Baseline Characteristics:

The mean standard deviation (SD) age of all participants was 47.3 (15.69) years. Eight (66.7%) participants were male, 7 (58.3%) were White by race, and 6 (50.0%) were Non-Hispanic or Latino by ethnicity.

The mean (SD) height of all participants was 171.9 (6.10) cm and the mean (SD) weight was 80.78 (5.35) kg of all participants. The reported mean body mass index (SD) was 27.37 (1.60) kg/m^2 among all participants.

Exposure:

In Period 1, the participants received a single vepdegestrant 200 mg dose [redacted], under fed conditions.

In Period 2, the participants received esomeprazole 40 mg once a day from Day 1 to Day 5 and a single vepdegestrant 200 mg dose [redacted] on Day 5, under fed conditions.

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Summary of Safety and PK Results

Safety Results:

Adverse Events:

No severe adverse events (AEs), serious adverse events (SAEs), or discontinuations due to AEs were reported in this study. All AEs were mild in severity.

Following the administration of a single dose vepdegestrant 200 mg in Period 1:

- 4 AEs were reported in 3 (25.0%) participants, 1 AE of which in 1 (8.3%) participant was assessed as treatment-related.
- AEs of vomiting, hunger, gastroenteritis, restlessness were all reported in 1 (8.3%) participant, of which hunger (1 [8.3%]) was considered as treatment-related.

Following the administration of esomeprazole 40 mg once a day from Day 1 to Day 4 in Period 2:

- 7 AEs were reported in 3 (25.0%) participants, 3 AEs of which in 2 (16.7%) participants were assessed as treatment-related.
- AEs of vision blurred, arthropod bite, muscle strain, dermatitis contact were all reported in 1 (8.3%) participant. None were assessed as treatment-related. Treatment-related AEs of headache were reported in 2 (16.7%) participants, among whom 1 (8.3%) participant also had a treatment-related AE of abdominal pain.

Following the administration of esomeprazole 40 mg with vepdegestrant 200 mg (coadministration in Period 2 Day 5):

- 1 AE of hunger was reported in 1 (8.3%) participant, which was assessed as treatment-related.

Deaths and SAEs:

No deaths or SAEs were reported in this study.

Dose Modifications and/or Discontinuations from Study Intervention or Study Due to AEs:

There was no dose interruption/dose reduction or discontinuation from study intervention or study due to AEs.

Clinical Laboratory Evaluations:

No laboratory abnormalities were considered clinically significant and reported as AEs by the investigator.

Other Safety Evaluations:

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No clinically meaningful findings in the vital signs measurements, ECGs, physical examination findings, or other observations related to safety were observed in this study.

PK Results:

Vepdegestrant Pharmacokinetics:

[redacted]

Co-administration of esomeprazole (40 mg QD for five days), a PPI, with a single dose of 200 mg vepdegestrant under fed condition decreased plasma vepdegestrant AUC_{inf} by 16% and C_{max} by 26% in healthy adult participants. The test/reference ratios of the adjusted geometric means (90% confidence interval [CI]) for vepdegestrant AUC_{inf} and C_{max} were 83.73% (76.32%, 91.86%) and 74.11% (63.47%, 86.52%), respectively, following vepdegestrant administration with esomeprazole (Test) as compared to administration alone (Reference).

[redacted]

CONCLUSIONS:

Pharmacokinetics

- Co-administration of esomeprazole (40 mg QD for five days), a PPI, with a single dose of 200 mg vepdegestrant under fed condition decreased plasma vepdegestrant AUC_{inf} by 16% and C_{max} by 26% in healthy adult participants. The test/reference ratios of the adjusted geometric means (90% CI) for vepdegestrant AUC_{inf} and C_{max} were 83.73% (76.32%, 91.86%) and 74.11% (63.47%, 86.52%), respectively, following vepdegestrant administration with esomeprazole (Test) as compared to administration alone (Reference).

Safety

- Vepdegestrant was safe and well-tolerated in healthy adult participants. No new safety signals were identified. No SAEs or discontinuations due to AEs were reported in this study. All AEs were mild in severity.

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