CLINICAL STUDY REPORT SYNOPSIS

Study Title:	An Interventional, Phase 1, Open-Label, Fixed Sequence, 2-Period Study to Estimate the Effect of Single and Multiple Doses of Vepdegestrant (ARV-471, PF-07850327) on the Pharmacokinetics of Single Dose Midazolam in Healthy Adult Females of Non-Childbearing Potential
Study Number:	C4891039
Study Phase:	1
Regulatory Agency or Public Disclosure Identifier Number:	EU CT Number: 2023-508518-40-00 ClinicalTrials.gov ID: NCT06256510
Pediatric Investigational Plan Number:	Not Applicable
Study Intervention:	Vepdegestrant
Study Sponsor:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Study Initiation Date (FPFV):	08 February 2024
Primary Completion Date (PCD):	16 April 2024
Presentation of data in this CSR based on: **Study Completion (LPLV) Date:**	13 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 / 19 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/countries of conduct, including the archiving of essential documents.

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

The study was conducted in the Pfizer clinical research unit (PCRU) in Belgium.

Publications:

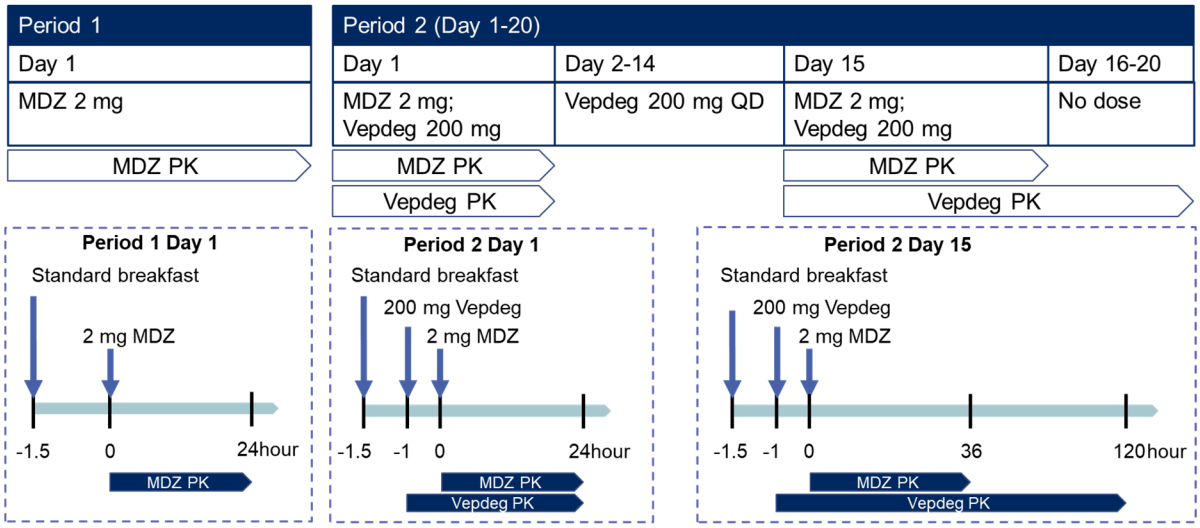
None.

Brief Description of the Trial Design and Methodology:

This was a Phase 1, open-label, 2-period, fixed-sequence study to estimate the effect of a single oral dose and multiple oral doses of vepdegestrant on the single-dose plasma pharmacokinetics (PK) of midazolam, a sensitive cytochrome P450 (CYP)3A4 substrate, in healthy female participants of non-childbearing potential.

This study consisted of 2 periods: in Period 1, participants were to receive a single dose of midazolam alone; in Period 2, participants were to receive a single dose of midazolam and a single dose of vepdegestrant on Day 1, multiple doses of vepdegestrant from Day 2 to Day 14, and a single dose of midazolam and a single dose of vepdegestrant on Day 15. A minimum washout period of 1 day occurred between the 2 successive single doses of midazolam on Period 1 Day 1 and Period 2 Day 1 in this study. Midazolam PK samples were collected up to 24 hours postdose on Period 1 Day 1 and Period 2 Day 1, and up to 36 hours postdose on Period 2 Day 15 after midazolam administration. Vepdegestrant PK samples were collected up to 24 hours postdose on Period 2 Day 1 and up to 120 hours postdose after vepdegestrant administration on Period 2 Day 15 (Figure S1).

Figure S1. Schema (Protocol C4891039)



MDZ = midazolam; Vepdeg = vepdegestrant (ARV-471, PF-07850327)

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Number of Participants (planned and analyzed):

Approximately 16 participants were to be enrolled in the study such that approximately 14 PK evaluable participants would complete the study. A total of 15 participants were enrolled and included in the safety and PK analysis sets.

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study enrolled healthy adult female participants of non-childbearing potential.

Study Intervention:

Participants received the following study interventions following standard breakfast:

- Midazolam: Single 2 mg dose on Study Day 1 of Period 1 approximately 1.5 hours (90 minutes) after the start of the breakfast; and on Study Days 1 and 15 of Period 2, approximately 1 hour (60 minutes) after vepdegestrant dosing.
- Vepdegestrant: Daily 200 mg doses on Study Days 1-15 of Period 2.

Midazolam, which is commercially available as an oral solution, was sourced locally by the PCRU. The investigational product (IP) information and manufacturing lot number for vepdegestrant dispensed in this study is provided in Table S1.

Table S1. Study Intervention Administered (Protocol C4891039)

IP Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
PF-07850327 (ARV-471) [redacted] mg [redacted]	20AR8805.HQ00006	23-DP-01506	[redacted] mg	Tablet

Global Substantial Modifications

Not applicable.

Global Interruptions and Re-Starts

Not applicable.

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Endpoints And Statistical Methods:

Table S2. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Missing Data	Analysis Model
Primary	**Primary:**				
• To evaluate and characterize the effect of multiple oral 200 mg once a day (QD) doses of vepdegestrant on the single dose PK of midazolam in healthy adult females of non-childbearing potential.	• Plasma midazolam PK parameters alone and following administration of 200 mg QD multiple doses (MD) of vepdegestrant: maximum plasma concentration (C_{max}), area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}) (if data permitted, otherwise area under the plasma concentration time profile from time zero to the time of the last quantifiable concentration [AUC_{last}]).	• Primary PK analysis	• PK Parameter Set	• Data were summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum. For appropriate PK parameters, geometric mean and geometric coefficient of variation (CV%) were also summarized. • Actual PK sampling times were used in the derivation of PK parameters. If a PK parameter couldn't be derived from a participant's concentration data, the parameter was coded as not calculated (NC). • In summary tables, statistics were not presented for a particular treatment group if more than 50% of the data were NC. For statistical analyses, PK parameters coded as NC were also set to missing, and statistics were presented for a	• Mixed effect model with treatment as a fixed effect and participant as a random effect

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Table S2. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Missing Data	Analysis Model
				particular treatment with >3 evaluable measurements.	
Secondary	**Secondary:**				
• To evaluate and characterize the effect of a single oral 200 mg dose of vepdegestrant on the single dose PK of midazolam in healthy adult females of non-childbearing potential.	• Plasma midazolam PK parameters alone and following administration of a 200 mg single dose (SD) of vepdegestrant: C_{max}, AUC_{inf} (if data permitted, otherwise AUC_{last}).	• Secondary PK analysis	• PK Parameter Set	• Same as for primary PK analysis	• Same as for primary PK analysis
• To characterize the effect of a single oral 200 mg dose and multiple oral 200 mg QD doses of vepdegestrant on the single dose PK of midazolam in healthy adult females of non-childbearing potential.	• Plasma midazolam PK parameters: AUC_{last}, time for C_{max} (T_{max}), terminal plasma elimination half-life ($t_{½}$), apparent clearance after oral dose (CL/F), apparent volume of distribution after oral dose (V_z/F) alone and after a single 200 mg dose and 200 mg QD MD of vepdegestrant, as data permitted.	• Secondary PK analysis	• PK Parameter Set	• Same as for primary PK analysis	• Same as for primary PK analysis
• To evaluate the safety and tolerability of vepdegestrant alone and in presence of midazolam in healthy adult females	• Assessment of adverse event (AE), safety laboratory tests, vital signs, and electrocardiograms (ECGs), and physical examination.	• Secondary safety analysis	• Safety Analysis Set	• Number of participants, numbers and percentages of participants meeting the categorical criteria were presented.	• Not applicable.

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Table S2. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Missing Data	Analysis Model
of non-childbearing potential.					

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SUMMARY OF RESULTS:

Participant Disposition

Of the 15 enrolled participants, 1 participant discontinued from the study during the treatment phase due to an AE and the remaining 14 participants completed the treatment phase as well as the follow-up (FU) phase.

Demographic and Other Baseline Characteristics:

All the 15 participants enrolled were White females, with a mean age of 63.5 years old and mean body mass index (BMI) of 25.5 kg/m^2.

Exposure:

Of the 15 participants, 14 received and completed their study interventions as planned, while the remaining 1 only received 1 dose of midazolam and did not enter into Period 2.

Summary of PK/Safety Results

PK Results

Median T_{max} was 1.00 hour when midazolam was co-administered with a single dose or multiple doses of vepdegestrant and after midazolam was administered alone. The mean $t_{½}$ was 6.135 hours and 7.561 hours when midazolam was co-administered with a single dose or multiple doses of vepdegestrant, respectively, and 5.482 hours when midazolam was administered alone. The CL/F of midazolam was 60.08 L/hour and 39.13 L/hour when midazolam was co-administered with a single dose or multiple doses of vepdegestrant, respectively, and 68.48 L/hour when midazolam was administered alone.

Following midazolam administration with a single dose of vepdegestrant (Test) as compared to midazolam administration alone (Reference), the Test/Reference ratios of the adjusted geometric means (90% confidence interval [CI]) for midazolam AUC_{inf}, AUC_{last}, and C_{max} were 106.32% (100.49%, 112.50%), 104.95% (99.85%, 110.31%), and 89.07% (81.06%, 97.87%), respectively.

Following midazolam administration with multiple doses of vepdegestrant (Test) as compared to midazolam administration alone (Reference), the Test/Reference ratios of the adjusted geometric means (90% CI) for midazolam AUC_{inf}, AUC_{last}, and C_{max} were 174.41% (158.61%, 191.77%), 174.74% (159.73%, 191.17%), and 115.01% (103.51%, 127.78%), respectively.

Similar inter-participant variability for AUC_{inf}, AUC_{last}, and C_{max} was observed when midazolam was co-administered with a single dose and multiple doses of vepdegestrant compared to when midazolam was administered alone. Geometric CV% of AUC_{inf}, AUC_{last}, and C_{max} ranged from 23-29%, 28-31%, and 22-29%, respectively.

Safety Results

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A total of 29 all-causality treatment-emergent AEs (TEAEs), all non-serious, were reported in 13 out of 15 participants (86.7%), and a total of 15 treatment-related TEAEs, all non-serious, were reported in 8 out of 15 participants (53.3%); none of the TEAEs were serious or severe, or resulted in dose reduction or dose interruption of any intervention in any period; 1 TEAE, not considered to be treatment-related by the investigator, resulted in the participant's discontinuation from the study intervention and the study during Period 1; no events of death were reported in the study.

TEAEs reported in the 2 periods are as follows (Note: events that occurred during the FU were counted as treatment-emergent and attributed to the last study intervention taken):

- Following the administration of midazolam alone on Period 1 Day 1, 6 all-causality preferred term (PT) TEAEs were reported in 5 out of 15 participants (33.3%), among which none of the TEAEs occurred in >2 participants; 1 TEAE of fatigue in 1 participant was considered to be treatment-related by the investigator.

- Following the administration of vepdegestrant and midazolam on Period 2 Day 1, 10 all-causality PT TEAEs were reported in 8 out of 14 participants (57.1%), among which none of the TEAEs occurred in >2 participants; 6 TEAEs including abdominal discomfort, abdominal pain, diarrhoea, and fatigue in 4 participants were considered to be treatment-related by the investigator.

- Following the administration of vepdegestrant during Period 2 Days 2 to 14, 13 all-causality PT TEAEs were reported in 9 out of 14 participants (64.3%), among which none but only 1 TEAE (constipation) occurred in >2 participants; 8 TEAEs including abdominal pain, constipation, diarrhoea, and headache in 5 participants were considered to be treatment-related by the investigator.

- Following the administration of vepdegestrant and midazolam on Period 2 Day 15, 1 all-causality PT TEAE was reported in 1 out of 14 participants (7.1%) and was not considered to be treatment-related by the investigator.

Out of the 15 participants, 11 (73.3%) participants had laboratory abnormalities (without regard to baseline abnormality) post any study intervention, where the most frequently reported (≥20%) abnormal parameters were in urinalysis, while none were considered clinically significant or reported as AEs.

No clinically meaningful findings in the vital signs measurements or ECGs were observed in this study.

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CONCLUSIONS:

PK

- Co-administration of multiple doses of vepdegestrant (200 mg once daily for 15 days) increased midazolam (2 mg oral dose) plasma exposure AUC_{inf} by 74%. Following midazolam administration with multiple doses of vepdegestrant (Test) as compared to midazolam administration alone (Reference), the Test/Reference ratios of the adjusted geometric means (90% CI) for midazolam AUC_{inf} and C_{max} were 174.41% (158.61%, 191.77%) and 115.01% (103.51%, 127.78%), respectively.

- Co-administration of a single dose of vepdegestrant (200 mg) had minimal impact on midazolam (2 mg oral dose) plasma exposure AUC_{inf}. Following midazolam administration with a single dose of vepdegestrant (Test) as compared to midazolam administration alone (Reference), the Test/Reference ratios of the adjusted geometric means (90% CI) for midazolam AUC_{inf} and C_{max} were 106.32% (100.49%, 112.50%) and 89.07% (81.06%, 97.87%), respectively.

Safety

- Vepdegestrant 200 mg QD alone for 14 days were generally safe and well tolerated in healthy adult female participants of nonchildbearing potential. No SAEs or severe AEs were reported in this study. No new safety issues were identified.

- One participant experienced a NSAE of cystitis (moderate severity, not related to the study interventions) following the administration of a single dose (2 mg) of midazolam alone and discontinued permanently from the study.

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