Poster PII-039

# The Effect of Carbamazepine on the Pharmacokinetics of Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader, in Healthy Adults

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## Objective

- To evaluate the effect of the strong cytochrome P450 (CYP)3A4 inducer carbamazepine on the pharmacokinetics (PK) of vepdegestrant (ARV-471) in healthy adult participants (NCT06005688)

## Key Findings

- In healthy adult participants (N=12), coadministration of a single dose of vepdegestrant 200 mg with multiple doses of carbamazepine decreased vepdegestrant area under the concentration-time curve (AUC) from time 0 extrapolated to infinity ($AUC_{inf}$) by 36% and maximum plasma concentration ($C_{max}$) by 20% compared with vepdegestrant administered alone
- The exposure of ARV-473 (the epimer of vepdegestrant) was similarly decreased (AUC from time 0 to the last quantifiable concentration [$AUC_{last}$] by 40% and $C_{max}$ by 25%)
- Vepdegestrant was well tolerated in healthy adult participants; no new safety signals were identified

## Conclusion

- Coadministration of multiple doses of carbamazepine, a strong CYP3A4 inducer, with a single dose of vepdegestrant resulted in a modest 36% decrease in plasma vepdegestrant exposure

**References**

**1.** Bekes M, et al. Nature Rev Drug Discov. 2022;21(3):181-200. **2.** Gough SM, et al. Clin Cancer Res. 2024;30(16):3549-63. **3.** Hamilton EP, et al. Presented at ESMO; October 20–24, 2023; Madrid, Spain. Poster 390P. **4.** Hurvitz SA, et al. Presented at SABCS; December 5–9, 2023; San Antonio, TX, USA. Poster PO3-05-08. **5.** Hamilton EP, et al. Future Oncol. 2024;20(32):2447-55. **6.** Datta-Mannan, et al. Clin Pharmacol Ther. 2024;116(4):1034-41. **7.** Food and Drug Administration US Department of Health and Human Services. M12 drug interaction studies. Updated August 2024. Accessed January 3, 2025. https://www.fda.gov/media/161199/download.

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## Background

- Vepdegestrant (ARV-471), an oral PROTAC estrogen receptor (ER) degrader, directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation[1,2]
- In a first-in-human phase 1/2 study (NCT04072952), vepdegestrant demonstrated a favorable safety profile and encouraging clinical activity[3,4]
  - Vepdegestrant 200 mg once daily was selected as the recommended phase 3 dose and is being evaluated as a monotherapy in the VERITAC-2 study (NCT05654623)[5]
- Based on in vitro data, vepdegestrant is metabolized by CYP3A4 (data on file); therefore, it is possible that administration of CYP3A4 inducers with vepdegestrant may lead to decreased plasma exposure of vepdegestrant
- Carbamazepine is a strong inducer of CYP3A4 and has been recommended by regulatory agencies as a probe to investigate CYP3A4 induction[6,7]
- This study (NCT06005688) was conducted to estimate the effect of carbamazepine on the PK of vepdegestrant and its epimer, ARV-473, in healthy adult participants

## Methods

- This study was performed at the Pfizer Clinical Research Unit (CRU) in Belgium in accordance with ethical principles from the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice. Approval was received from the local independent ethics committee, and all local requirements were followed

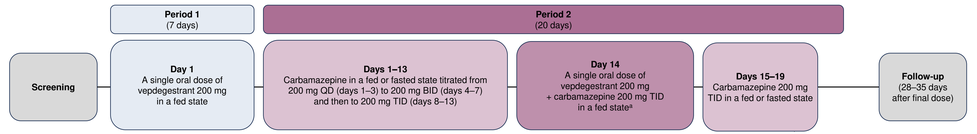
### Participants

- Eligible participants included healthy male and female adults (≥18 years old) of non-childbearing potential as determined by medical evaluation with a body mass index of 16–32 kg/m$^2$ and a total body weight >45 kg
  - Exclusion criteria included but were not limited to evidence or history of clinically significant conditions, positivity for genotyping markers related to Stevens-Johnson syndrome or toxic epidermal necrolysis (HLA-B*1502 and/or HLA-A*3101), use of moderate or strong CYP3A inducers and inhibitors within 14 days plus 5 half-lives prior to the first dose of study intervention, and use of prescription or nonprescription medications within 7 days prior to the first dose of study intervention

### Study Design

- This study was a phase 1, open-label, fixed-sequence, 2-period study in healthy adults who were confined to the CRU on days 1–4 in period 1 (confinement was optional on days 5–7 in period 1) and days 1–20 in period 2 (**Figure 1**)
- In period 1, participants received a single oral dose of vepdegestrant 200 mg alone in a fed state; in period 2, carbamazepine dosing was titrated from 200 mg once daily (QD; on days 1–3) to 200 mg twice daily (BID; on days 4–7) and then to 200 mg three times daily (TID; on days 8–19), with a single oral dose of vepdegestrant 200 mg administered in a fed state on day 14 of period 2

### Figure 1: Study design




To determine vepdegestrant and ARV-473 PK parameters, serial blood PK samples were collected predose and at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours post vepdegestrant dose in period 1 (single dose of vepdegestrant alone) and in period 2 (single dose of vepdegestrant and multiple doses of carbamazepine)

Vepdegestrant was administered as 2 tablets of 100 mg approximately 30 minutes after the start of a standard breakfast. Carbamazepine was administered as 1 tablet of 200 mg with or without food.
*The morning dose of carbamazepine on day 14 of period 2 was administered in a fed state approximately 30 minutes after the start of a standard breakfast, followed within 5 minutes by administration of the single oral dose of vepdegestrant 200 mg.
BID=twice daily; PK=pharmacokinetic; QD=once daily; TID=three times daily.

### Assessment and Analysis

- Plasma concentrations of vepdegestrant and ARV-473 were determined using a validated, sensitive, high-performance liquid chromatography tandem mass spectrometric method at Labcorp Development (Asia) Pte. Ltd. (Singapore)
- Participants underwent physical examinations and were monitored for adverse events (AEs), vital signs, and electrocardiogram changes throughout the study, including during follow-up or early termination/discontinuation visits. Blood samples for safety laboratory analyses were collected before vepdegestrant dosing (day −1) and 24 hours post dose (day 2) in period 1 and before (day −1) and during (days 3, 6, 9, and 13) carbamazepine dosing in period 2, as well as 24 hours and 144 hours after the single vepdegestrant dose on day 14 in period 2
- Vepdegestrant and ARV-473 PK parameters were estimated using a noncompartmental approach. Natural log–transformed PK parameters of vepdegestrant ($AUC_{inf}$ and $C_{max}$) and ARV-473 ($AUC_{last}$ and $C_{max}$) were analyzed using a mixed-effects model with treatment as a fixed effect and participant as a random effect
  - Estimates of the adjusted mean differences of the test treatment (period 2, vepdegestrant in the presence of carbamazepine) and the reference treatment (period 1, vepdegestrant alone) were obtained from the model and exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference)

## Results

### Demographics and Baseline Characteristics

- Baseline characteristics of the 12 healthy adult male participants enrolled and treated in the study are shown in **Table 1**
- All participants were included in the PK and safety analyses

**Table 1: Demographics and baseline characteristics**

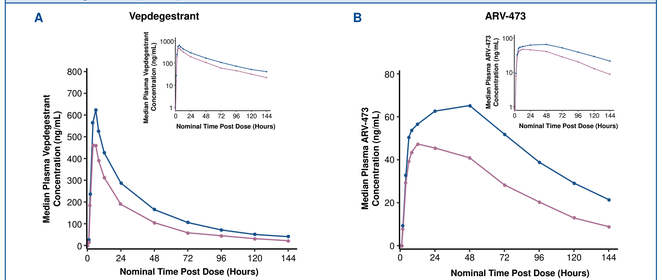
| Characteristic | Participants (N=12) |
|---|---|
| Age, years, median (range) | 39.5 (22.0–59.0) |
| Sex, male, n (%) | 12 (100.0) |
| Race, n (%) | |
| White | 9 (75.0) |
| Black or African American | 1 (8.3) |
| Asian | 1 (8.3) |
| Not reported | 1 (8.3) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 2 (16.7) |
| Not Hispanic or Latino | 10 (83.3) |
| BMI, kg/m$^2$, median (range) | 23.8 (22.3–29.4) |
| Weight, kg, median (range) | 75.8 (66.9–91.2) |

BMI=body mass index.

### Pharmacokinetics

- The plasma concentration-time profiles of vepdegestrant and ARV-473 with and without carbamazepine are presented in **Figure 2**
- Summaries of vepdegestrant and ARV-473 PK parameters with and without carbamazepine are presented in **Table 2** and displayed in **Figure 3**
- Vepdegestrant $AUC_{inf}$ and $C_{max}$ following multiple doses of carbamazepine decreased by 36% and 20%, respectively
- Median time to reach $C_{max}$ ($T_{max}$) was 6.0 hours when vepdegestrant was administered alone and when administered with carbamazepine
- Terminal plasma elimination half-life ($t_{1/2}$) was 50.1 hours when vepdegestrant was administered alone and 45.4 hours when administered with carbamazepine
- Similarly, coadministration of carbamazepine with vepdegestrant resulted in a decrease in ARV-473 exposure

### Figure 2: Median plasma (A) vepdegestrant and (B) ARV-473 concentrations versus time on linear scales and semi-log scales (insets)



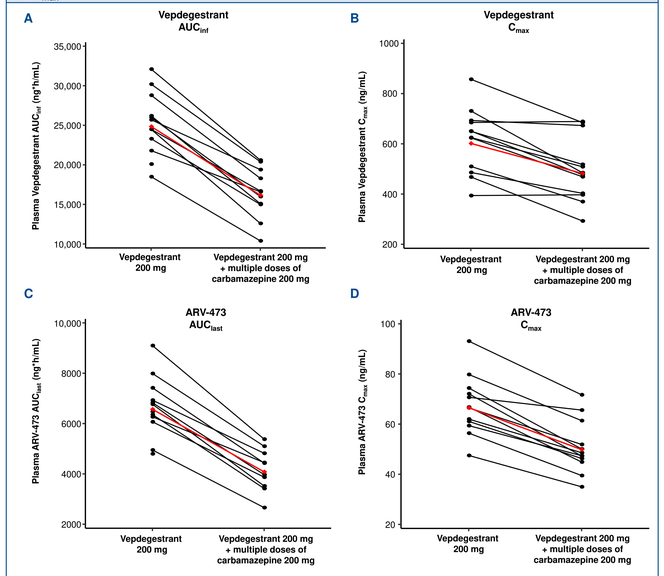

Data are from the PK parameter analysis set, which includes participants who received ≥1 dose of study intervention and had ≥1 PK parameter of interest.
PK=pharmacokinetic.

### Table 2: Descriptive summary of plasma vepdegestrant and ARV-473 PK parameters

| PK parameter[a] | n | Vepdegestrant 200 mg Reference | n | Vepdegestrant 200 mg + multiple doses of carbamazepine 200 mg Test | Ratio of adjusted geometric means (90% CI)[b] Test/reference |
|---|---|---|---|---|---|
| **Vepdegestrant** | | | | | |
| $AUC_{inf}$, ng*h/mL | 12 | 24,850 (16) | 11 | 16,160 (21) | 64.1 (60.0–68.4) |
| $C_{max}$, ng/mL | 12 | 601.5 (22) | 12 | 482.1 (27) | 80.2 (74.0–86.8) |
| $T_{max}$, h | 12 | 6.0 (2.0–6.0) | 12 | 6.0 (4.0–7.8) | - |
| $t_{1/2}$, h | 12 | 50.1 ± 4.0 | 11 | 45.4 ± 9.2 | - |
| CL/F, L/h | 12 | 8.0 (16) | 11 | 12.4 (21) | - |
| $V_z$/F, L | 12 | 579.1 (19) | 11 | 793.5 (25) | - |
| **ARV-473** | | | | | |
| $AUC_{last}$, ng*h/mL | 12 | 6568 (18) | 10 | 4081 (22) | 60.4 (56.8–64.3) |
| $C_{max}$, ng/mL | 12 | 66.6 (18) | 12 | 49.8 (21) | 74.9 (71.3–78.7) |
| $T_{max}$, h | 12 | 24.0 (23.2–48.0) | 12 | 12.0 (7.8–23.3) | - |
| $t_{1/2}$, h | 6 | 48.9 ± 5.1 | 10 | 43.8 ± 5.7 | - |

Data are from the PK parameter analysis set, which includes participants who received ≥1 dose of the study drug and have ≥1 PK parameter of interest.
[a]Data are presented as geometric mean (CV%) except for $T_{max}$, which is presented as median (range), and $t_{1/2}$, which is presented as arithmetic mean ± standard deviation.
[b]Ratios and 90% CIs are expressed as percentages.
AUC=area under the plasma concentration-time curve; $AUC_{inf}$=AUC from time 0 extrapolated to infinity; $AUC_{last}$=AUC from time 0 to the time of the last quantifiable concentration; CL/F=apparent oral clearance; $C_{max}$=maximum plasma concentration; CV%=percent coefficient of variation; PK=pharmacokinetic; $t_{1/2}$=terminal elimination half-life; $T_{max}$=time to reach $C_{max}$; $V_z$/F=apparent volume of distribution.

### Figure 3: Individual and geometric mean (A) $AUC_{inf}$ and (B) $C_{max}$ of vepdegestrant and (C) $AUC_{last}$ and (D) $C_{max}$ of ARV-473 by treatment




Data are from the PK parameter analysis set, which includes participants who received ≥1 dose of study intervention and have ≥1 PK parameter of interest. Red data points indicate geometric mean for each parameter. Black data points indicate individual values.
AUC=area under the plasma concentration-time curve; $AUC_{inf}$=AUC from time 0 extrapolated to infinity; $AUC_{last}$=AUC from time 0 to the time of the last quantifiable concentration; $C_{max}$=maximum plasma concentration; PK=pharmacokinetic.

### Safety

- A total of 9 treatment-emergent AEs (TEAEs) were reported in 6 (50.0%) participants following a single dose of vepdegestrant, 55 TEAEs were reported in 12 (100%) participants following multiple doses of carbamazepine alone, and 20 TEAEs were reported in 9 (75.0%) participants following a single dose of vepdegestrant with multiple doses of carbamazepine
- Following a single dose of vepdegestrant, 2 (16.7%) participants experienced treatment-related AEs (1 event each); both were mild (**Table 3**)
- There were no severe or serious AEs (SAEs) and no discontinuations due to AEs following administration of vepdegestrant alone
- Following administration of a single dose of vepdegestrant with multiple doses of carbamazepine, 2 SAEs of increased hepatic enzyme levels were reported in 2 participants (16.7%); these SAEs were assessed as not related to vepdegestrant and resolved
  - Both participants discontinued from the study; one due to the SAE of liver function test increased and the other due to a nonserious AE of moderate maculopapular rash
- No clinically relevant findings were observed for laboratory measurements, electrocardiograms, vital sign assessments, or physical exams

**Table 3: Summary of TRAEs**

| AEs by preferred term, n (%) | Vepdegestrant 200 mg (N=12) | Multiple doses of carbamazepine 200 mg (N=12) | Vepdegestrant 200 mg + multiple doses of carbamazepine 200 mg (N=12) |
|---|---|---|---|
| Any TRAE | 2 (16.7) | 0 | 0 |
| Diarrhea | 1 (8.3) | 0 | 0 |
| Somnolence | 1 (8.3) | 0 | 0 |

Data are from the safety analysis set, which includes participants who received ≥1 dose of vepdegestrant or carbamazepine. The treatment column reflects the study treatment at the time of the AE.
AE=adverse event; TRAE=treatment-related AE.