Poster 212

A Relative Bioavailability Study of Vepdegestrant Tablets in Healthy Adult Participants

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Objective

- To estimate the relative oral bioavailability of a single 200 mg dose of commercially representative vepdegestrant tablets compared with a single 200 mg dose of the pivotal phase 3 vepdegestrant tablets in healthy adults

Key Findings

- Both commercially representative tablets met bioequivalence criteria relative to the pivotal phase 3 tablet, with the 90% CIs of the test/reference ratios for the maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve from time 0 to infinity (AUC_{inf}) falling completely within the bioequivalence limits (80.00%–125.00%)
- Treatment-related adverse event (TRAE) rates were similar (4%–6%) across the tablet formulations

Conclusion

- Commercially representative vepdegestrant tablets demonstrated bioequivalence with the vepdegestrant tablets used in the pivotal phase 3 VERITAC-2 study
- Single doses of vepdegestrant 200 mg were well tolerated with no new safety signals, and each tablet formulation demonstrated a similar safety profile in healthy adult participants

References

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Disclosures

DZY, KTM, JAW, KCL, and WT are employees of Pfizer, Inc. YZ is an employee of Arvinas Operations, Inc.

Acknowledgments

We thank the volunteers who participated in this study.
This study was sponsored by Pfizer, Inc., in collaboration with Arvinas Estrogen Receptor, Inc. Medical writing support was provided by Genevieve R. Curtis, PhD, of Red Nucleus and funded by Arvinas Operations, Inc.

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Annual Meeting of the American College of Clinical Pharmacology (ACCP), Phoenix, AZ, September 14–16, 2025

Background

- Vepdegestrant, an oral PROteolysis TArgeting Chimera (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]
- Based on results from the first-in-human phase 1/2 study (NCT04072952) in patients with ER-positive (ER+)/human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer, vepdegestrant 200 mg once daily (QD) was selected as the phase 3 dose[3-5]
- In the recent pivotal phase 3 VERITAC-2 study (NCT05654623), vepdegestrant 200 mg QD significantly prolonged progression-free survival compared with fulvestrant in previously treated patients with ER+/HER2- advanced breast cancer harboring mutations in the estrogen receptor 1 gene and demonstrated a favorable safety profile.[6] The 200 mg QD dose is now the proposed dose for the treatment of ER+/HER2- advanced breast cancer
- This phase 1 study (NCT06347861) was conducted to estimate the relative bioavailability of a single oral 200 mg dose of vepdegestrant in healthy adults administered in 2 commercially representative tablet formulations compared with the tablet used in the pivotal phase 3 VERITAC-2 study

Methods

- This study was conducted in a clinical research unit in the United States 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 local independent ethics committees, and all local requirements were followed
- This relative bioavailability study was conducted using bioequivalence standards and adhered to bioequivalence study requirements with prespecified criteria supporting claims of bioequivalence

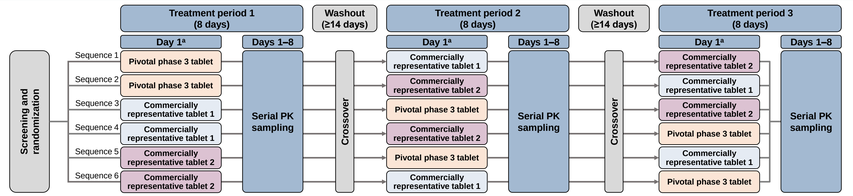
Participants

- Eligible participants were healthy adult (≥18 years old) males and females (of non-childbearing potential) with a body mass index of 16–32 kg/m^2 and total body weight >45 kg (99.2 lb)
- Key exclusion criteria were evidence or history of clinically significant conditions, any relevant medical or psychiatric condition, and any use of prescription or nonprescription medications within 7 days or 5 half-lives (whichever was longer) prior to the first dose of study intervention
  - Use of moderate or strong cytochrome P450 3A (CYP3A) inducers was prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention
  - Use of moderate or strong CYP3A inhibitors was prohibited within 14 days or 5 half-lives prior to the first dose of study intervention

Study Design

- This was a phase 1, randomized, open-label, 3-period, 3-treatment, 6-sequence, crossover, single-dose study in healthy adult participants
- Each of the 3 treatments investigated in this study was a single 200 mg dose of vepdegestrant administered as
  - **Pivotal phase 3 tablet (reference):** 2 × 100 mg pivotal phase 3 tablets
  - **Commercially representative tablet 1 (test):** 2 × 100 mg commercially representative tablets
  - **Commercially representative tablet 2 (test):** 1 × 200 mg commercially representative tablet
- Vepdegestrant tablets were administered following a high-fat and high-calorie meal
- Enrolled participants were randomly assigned to 1 of 6 treatment sequences to receive all 3 treatments, with 1 treatment administered in each period. Treatment periods were separated by a washout period of at least 14 days between 2 successive doses of vepdegestrant (**Figure 1**)

Figure 1: Study design



Serial blood PK samples were collected predose and at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hours following vepdegestrant dosing in each period.

For each study period, participants were admitted to the CRU on the day before initiating treatment (day −1; check-in) and remained through completion of the day 8 assessment. Pivotal phase 3 tablet: 2 × 100 mg pivotal phase 3 tablets. Commercially representative tablet 1: 2 × 100 mg commercially representative tablets. Commercially representative tablet 2: 1 × 200 mg commercially representative tablet.
[a]All treatments were administered after an overnight fast of at least 10 hours, followed by a high-fat and high-calorie breakfast approximately 30 minutes prior to dosing.
CRU=clinical research unit; PK=pharmacokinetic.

Assessment and Analysis

- Plasma concentrations of vepdegestrant were determined using a validated, sensitive, high-performance liquid chromatography–tandem mass spectrometric method at LabCorp Development (Asia) Pte. Ltd. (Singapore)
- Vepdegestrant pharmacokinetic (PK) parameters were estimated using noncompartmental analysis of plasma concentration–time data. Natural log–transformed C_{max}, AUC from time 0 to 72 hours (AUC_{72}), AUC from time 0 to 168 hours (AUC_{168}), and AUC_{inf} were analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and participant within a sequence as a random effect
  - Estimates of the adjusted mean differences of the test treatments (commercially representative tablets) and the reference treatment (pivotal phase 3 tablet) and the corresponding 90% CIs were obtained from the model and exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% CI for the ratios
- Bioequivalence was to be declared if the 90% CIs of the ratio of adjusted geometric means for C_{max} and AUC_{inf} fell completely within the range of 80.00%–125.00%
- Participants underwent physical exams and were monitored for AEs, vital signs, and electrocardiogram (ECG) changes throughout the study, including at follow-up or early termination/discontinuation visits. Blood samples for safety laboratory analyses were collected before vepdegestrant dosing and throughout the study

Results

Demographics and Baseline Characteristics

- Baseline characteristics of the 52 healthy adult participants enrolled and treated in the study are shown in **Table 1**
  - All participants were included in the PK and safety analyses
  - Of the randomized participants, 45 (86.5%) completed the study, and no participants discontinued due to AEs
- Overall, 49 (94.2%) participants received the pivotal phase 3 tablets, 50 (96.2%) received commercially representative tablet 1, and 49 (94.2%) received commercially representative tablet 2

Table 1: Demographics and baseline characteristics

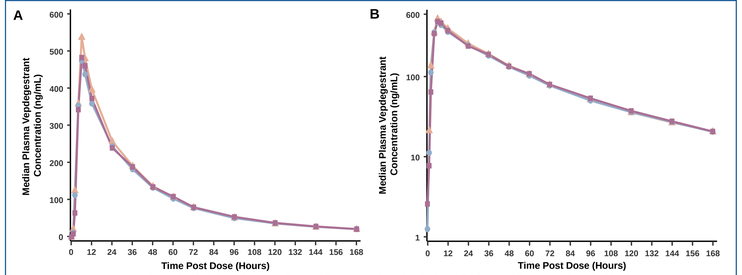
Characteristic	Participants (N=52)
Age, years, median (range)	48.5 (23.0–69.0)
Sex, n (%)	
Male	38 (73.1)
Female	14 (26.9)
Race, n (%)	
White	35 (67.3)
Black or African American	7 (13.5)
Asian	6 (11.5)
American Indian or Alaska Native	2 (3.8)
Multiracial	2 (3.8)
Ethnicity, n (%)	
Not Hispanic or Latino	46 (88.5)
Hispanic or Latino	6 (11.5)
BMI, kg/m^2, median (range)	27.8 (20.7–32.0)
Weight, kg, median (range)	81.7 (56.0–112.5)

BMI=body mass index.

Pharmacokinetics

- Following single oral doses of vepdegestrant 200 mg in the fed state, median plasma vepdegestrant concentration–time profiles for the pivotal phase 3 tablet and both commercially representative tablets were nearly superimposable (**Figure 2**)
- Summaries of PK parameters for each vepdegestrant treatment are presented in **Table 2**
- The 90% CIs for the test/reference ratios of C_{max} and AUC_{inf} for commercially representative tablet 1 and commercially representative tablet 2 relative to the pivotal phase 3 tablet fell completely within the bioequivalence limits (80.00%–125.00%; **Table 3**)

Figure 2: Median plasma vepdegestrant concentrations versus time on (A) linear scales and (B) semi-log scales by treatment



Data are from the PK parameter analysis set, which includes all participants who received ≥1 dose of vepdegestrant and have ≥1 parameter of interest for vepdegestrant. Pivotal phase 3 tablet: 2 × 100 mg pivotal phase 3 tablets. Commercially representative tablet 1: 2 × 100 mg commercially representative tablets. Commercially representative tablet 2: 1 × 200 mg commercially representative tablet.
PK=pharmacokinetic.

Table 2: Descriptive summary of plasma PK parameters for vepdegestrant

PK parameter[a]	n	Pivotal phase 3 tablet Reference	n	Commercially representative tablet 1 Test	n	Commercially representative tablet 2 Test
C_{max}, ng/mL	48	549.6 (26)	50	523.5 (27)	49	507.8 (25)
AUC_{inf}, ng*h/mL	48	21,260 (25)	50	20,620 (23)	48	20,510 (21)
AUC_{168}, ng*h/mL	47	19,510 (25)	50	18,910 (23)	48	18,830 (21)
AUC_{72}, ng*h/mL[b]	48	15,480 (25)	50	14,940 (23)	49	14,690 (22)
CL/F, L/h	48	9.4 (25)	50	9.7 (23)	48	9.7 (21)
$t_{1/2}$, h	48	56.0 ± 8.3	50	56.3 ± 7.1	48	54.6 ± 6.3
T_{max}, h	48	6.0 (4.0–12.0)	50	6.0 (4.0–12.0)	49	6.0 (4.0–12.0)
Vz/F, L	48	752.5 (29)	50	780.9 (26)	48	763.5 (26)

Data are from the PK parameter analysis set, which includes all participants who received ≥1 dose of vepdegestrant and have ≥1 PK parameter of interest for vepdegestrant. Pivotal phase 3 tablet: 2 × 100 mg pivotal phase 3 tablets. Commercially representative tablet 1: 2 × 100 mg commercially representative tablets. Commercially representative tablet 2: 1 × 200 mg commercially representative tablet.
[a]Data are presented as geometric mean (CV%) for all parameters except for T_{max} which is presented as median (range), and $t_{1/2}$ which is presented as arithmetic mean ± standard deviation.
[b]Truncated AUC_{72} was derived to comply with the ICH M13A guideline for bioequivalence for immediate-release solid oral dosage forms (released July 23, 2024).[7]
AUC_{72}=area under the plasma concentration–time curve from time 0 to 72 hours; AUC_{168}=area under the plasma concentration–time curve from time 0 to 168 hours; AUC_{inf}=area under the plasma concentration–time curve from time 0 extrapolated to infinity; CL/F=apparent oral clearance; C_{max}=maximum plasma concentration; CV%=percent coefficient of variation; ICH=International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; PK=pharmacokinetic; $t_{1/2}$=terminal elimination half-life; T_{max}=time to reach C_{max}; Vz/F=apparent volume of distribution.

Table 3: Statistical summary of log-transformed PK parameters for vepdegestrant

PK parameter	n Test	n Reference	Adjusted geometric means Test	Adjusted geometric means Reference	Ratio of adjusted geometric means (90% CI)[a] Test/reference
Commercially representative tablet 1 (test) versus pivotal phase 3 tablet (reference)					
C_{max}, ng/mL	50	48	519.5	544.6	95.40 (91.00–100.01)
AUC_{inf}, ng*h/mL	50	48	20,740	21,320	97.28 (94.40–100.26)
AUC_{168}, ng*h/mL	50	47	19,030	19,630	96.98 (93.98–100.07)
AUC_{72}, ng*h/mL[b]	50	48	14,930	15,370	97.15 (93.87–100.53)
Commercially representative tablet 2 (test) versus pivotal phase 3 tablet (reference)					
C_{max}, ng/mL	49	48	502.3	544.6	92.23 (87.97–96.69)
AUC_{inf}, ng*h/mL	48	48	20,400	21,320	95.68 (92.84–98.61)
AUC_{168}, ng*h/mL	48	47	18,720	19,630	95.40 (92.45–98.44)
AUC_{72}, ng*h/mL[b]	49	48	14,560	15,370	94.79 (91.59–98.10)

Data are from the PK parameter analysis set, which includes all participants who received ≥1 dose of vepdegestrant and have ≥1 PK parameter of interest for vepdegestrant. Pivotal phase 3 tablet: 2 × 100 mg pivotal phase 3 tablets. Commercially representative tablet 1: 2 × 100 mg commercially representative tablets. Commercially representative tablet 2: 1 × 200 mg commercially representative tablet.
[a]The ratio of adjusted geometric means and 90% CI are expressed as percentages.
[b]Truncated AUC_{72} was derived to comply with the ICH M13A guideline for bioequivalence for immediate-release solid oral dosage forms (released July 23, 2024).[7]
AUC_{72}=area under the plasma concentration–time curve from time 0 to 72 hours; AUC_{168}=area under the plasma concentration–time curve from time 0 to 168 hours; AUC_{inf}=area under the plasma concentration–time curve from time 0 extrapolated to infinity; C_{max}=maximum plasma concentration; ICH=International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; PK=pharmacokinetic.

Safety

- Overall, treatment-emergent AEs (TEAEs) were reported in 10 (20.4%) participants receiving the pivotal phase 3 tablets, 13 (26.0%) participants receiving commercially representative tablet 1, and 12 (24.5%) participants receiving commercially representative tablet 2
- The majority of TEAEs were mild in severity; no AEs reported during the study were severe, serious, or led to treatment discontinuation
- TRAEs occurred in 2 (4.1%) participants receiving the pivotal phase 3 tablets, 3 (6.0%) receiving commercially representative tablet 1, and 2 (4.1%) receiving commercially representative tablet 2
- The most common TRAE was diarrhea, reported in 2 participants following treatment with commercially representative tablet 1 and 1 participant with commercially representative tablet 2
  - Three TRAEs were considered moderate in severity: increased alanine aminotransferase and increased aspartate aminotransferase in 1 participant receiving the pivotal phase 3 tablet and dyspnea in 1 participant receiving commercially representative tablet 1
- No clinically meaningful changes in laboratory tests, vital signs, or ECGs were observed during the study, and findings were similar across the treatment groups