Poster PII-157

The Effect of Itraconazole on the Pharmacokinetics of Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader in Healthy Adult Participants

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Objective

- To evaluate the impact of itraconazole, a strong cytochrome P450 (CYP)3A inhibitor, on the pharmacokinetics (PK) of vepdegestrant (ARV-471) in healthy adult participants (NCT05538312)

Key Findings

- In healthy adult participants (N=12), co-administration of a single dose of vepdegestrant (200 mg) with multiple doses of itraconazole (200 mg) increased vepdegestrant plasma area under the concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}) by 69% and maximum plasma concentration (C_{max}) by 52%
  - The exposure of ARV-473 (the epimer metabolite of vepdegestrant) was increased to a similar extent as vepdegestrant (area under the concentration-time curve from time 0 to 120 hours [AUC_{120}] by 62% and C_{max} by 53%)
- Treatment-emergent adverse events (TEAEs) occurred in 2 (16.7%) participants after vepdegestrant treatment, 3 (25.0%) participants after itraconazole treatment, and 2 (16.7%) participants after vepdegestrant and itraconazole combination treatment
- Treatment-related adverse events (TRAEs) occurred in 1 (8.3%) participant after vepdegestrant treatment (abdominal pain and diarrhea)

Conclusions

- Co-administration of multiple doses of the potent CYP3A inhibitor itraconazole modestly increased vepdegestrant exposure
  - Dose reduction of vepdegestrant when co-administered with strong CYP3A inhibitors should be considered to achieve similar vepdegestrant exposure when administered without strong CYP3A inhibitors
- The study treatments were well tolerated in healthy adult participants; no new safety issues were identified

References

1. Flanagan JJ, et al. Presented at SABCS; Dec 4-8, 2018; San Antonio, TX. Poster P5-04-18. **2.** Hurvitz SA, et al. Presented at SABCS; Dec 5-9, 2023; San Antonio, TX. Poster PO3-05-08. **3.** Hamilton EP, et al. Presented at SABCS; Dec 5-9, 2023; San Antonio, TX. Poster PS15-03. **4.** Hamilton EP, et al. Presented at ESMO; Oct 20-24, 2023; Madrid, Spain. Poster 390P. **5.** Campone M, et al. Presented at SABCS; Dec 5-9, 2023; San Antonio, TX. Poster PO1-19-12. **6.** Wander SA, et al. Presented at SABCS; Dec 5-9, 2023; San Antonio, TX. Poster PO2-20-03. **7.** Itraconazole. Prescribing information. Janssen Pharmaceuticals, Inc.; 2023. **8.** EMA. Accessed Mar 12, 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf. **9.** FDA. M12 drug interaction studies. Accessed Mar 12, 2024. https://www.fda.gov/media/161199/download.

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Background

- Vepdegestrant (ARV-471) is a selective, orally administered PROTAC estrogen receptor (ER) degrader that directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation[1]
- In the first-in-human phase 1/2 study (NCT04072952), vepdegestrant was well tolerated and had encouraging clinical activity in patients with ER-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer[2-4]
- Vepdegestrant 200 mg once daily (QD) is currently under clinical development in 2 phase 3 studies as monotherapy and in combination with palbociclib for patients with ER+/HER2- advanced breast cancer[5,6]
- Based on in vitro data, vepdegestrant is metabolized by CYP3A (data on file); therefore, it is possible that administration of CYP3A inhibitors with vepdegestrant may lead to increased plasma exposure of vepdegestrant
- Itraconazole, a synthetic triazole antifungal agent, and its primary metabolite hydroxy-itraconazole are strong inhibitors of CYP3A4[7]; therefore, itraconazole has been recommended as a probe to investigate CYP3A inhibition by regulatory agencies[8,9]
- This study (NCT05538312) was conducted to estimate the effect of itraconazole on the PK of vepdegestrant and its epimer ARV-473 following a single oral dose of vepdegestrant 200 mg with and without co-administration of multiple doses of itraconazole 200 mg QD in healthy adult participants

Methods

- This study was conducted at the Pfizer Clinical Research Unit (CRU) in Belgium in compliance with the ethical principles outlined in the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines. Approval was received from the local Independent Ethics Committee, and all local regulatory requirements were followed

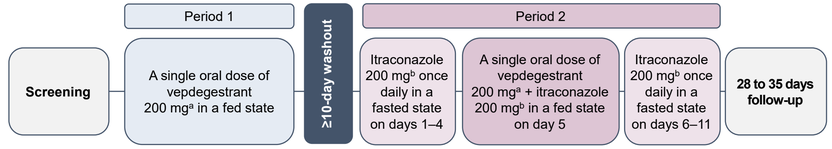
Participants

- Eligible participants included females (of non-childbearing potential) and males who were overtly healthy as determined by medical evaluation between the ages of 18–65 years with body mass index of 17.5-30.5 kg/m^2 and total body weight >50 kg
- Exclusion criteria included but were not limited to evidence or history of clinically significant conditions and use of prescription or nonprescription medications within 7 days prior to first dose of study intervention. Moderate or strong CYP3A inducers and inhibitors were prohibited within 14 days plus 5 half-lives and 14 days or 5 half-lives (whichever was longer), respectively, prior to the first dose of study intervention

Study Design

- This was a phase 1, open-label, 2-period, fixed-sequence study in healthy adults (**Figure 1**). Participants were not required to remain in the unit between the periods. In period 2, participants were admitted to the CRU on the day prior to itraconazole dosing (day −1) and remained at the CRU through day 12 at the discretion of the investigator
- Healthy adult participants received 2 single doses of vepdegestrant. The first dose was administered alone (period 1) followed by at least 10 days of washout. The second dose was administered concurrently with itraconazole on day 5 in period 2. A high fat, high calorie breakfast was provided in period 1 and in period 2 on day 5

Figure 1: Study design



To determine the 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, and 120 hours post vepdegestrant dose in period 1 (vepdegestrant alone) and predose and at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post vepdegestrant and itraconazole doses in period 2 (vepdegestrant + itraconazole)

[a]Administered as 2 tablets of 100 mg within ≈10 minutes of completion of a standard high fat meal
[b]Administered as 20 mL of a 10 mg/mL solution
PK=pharmacokinetics

Assessment and Analyses

- Vepdegestrant and ARV-473 PK parameters were estimated using a noncompartmental approach. Natural log–transformed PK parameters of vepdegestrant (C_{max} and AUC_{inf}) and ARV-473 (C_{max} and AUC_{120}) were analyzed using a mixed-effects model, which included sequence, period, and treatment as fixed effects and participant as a random effect
  - AUC_{120} was also provided and used in the statistical summary to compare AUC_{120} values of the test treatment (period 2; vepdegestrant + itraconazole) and the reference treatment (period 1; vepdegestrant alone) to account for the difference in sampling intervals between test treatment (0–168 hours) and reference treatment (0–120 hours)
- Plasma concentrations of vepdegestrant and ARV-473 were determined by a validated, sensitive, and specific high-performance liquid chromatography-tandem mass spectrometric (HPLC-MS/MS) method at LabCorp Development (Asia) Pte. Ltd. (Singapore)
- Participants underwent physical examinations and were monitored for adverse events (AEs), vital signs, and electrocardiogram (ECG) changes throughout the study, including follow-up or early termination/discontinuation. Blood samples for safety laboratories were collected at screening and on day −1 of period 1 (admission), day 4, and last day of each period

Results

Demographics and Baseline Characteristics

- Baseline characteristics of the 12 healthy adult 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

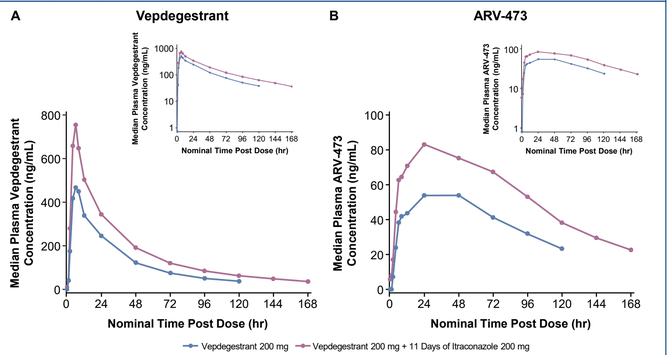
Characteristic	Total (N=12)
Age, median (range), y	37 (24–60)
Sex, n (%)	
Female	1 (8.3)
Male	11 (91.7)
Race, n (%)	
Asian	1 (8.3)
Black or African American	3 (25.0)
White	8 (66.7)
Ethnicity, n (%)	
Not Hispanic or Latino	12 (100)
BMI, median (range), kg/m^2	26.4 (21.3–30.1)
Weight, median (range), kg	75.2 (67.8–96.0)

BMI=body mass index

Pharmacokinetics

- The plasma concentration-time profiles of vepdegestrant and ARV-473 with and without itraconazole are presented in **Figure 2**
- Summaries of vepdegestrant PK parameters with and without itraconazole are presented in **Table 2** and displayed in **Figure 3**
  - Vepdegestrant AUC_{inf} and C_{max} following multiple doses of itraconazole increased by 69% and 52%, respectively
    - Interparticipant variability in vepdegestrant exposure based on AUC_{inf} and C_{max} was similar when vepdegestrant was administered alone (23% and 22%, respectively) and when administered with itraconazole (24% and 19%, respectively)
  - Median time to reach C_{max} (T_{max}) was 6.0 hours when vepdegestrant was administered alone and when administered with itraconazole
  - Apparent first-order terminal elimination half-life ($t_{1/2}$) was longer when vepdegestrant was administered with itraconazole (61.6 hours) than when vepdegestrant was administered alone (42.6 hours)
- The exposure of ARV-473 was increased to a similar extent as vepdegestrant following vepdegestrant co-administration with multiple doses of itraconazole (**Table 2; Figure 3**); median T_{max} and terminal $t_{1/2}$ were also longer with itraconazole (**Table 2**)

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



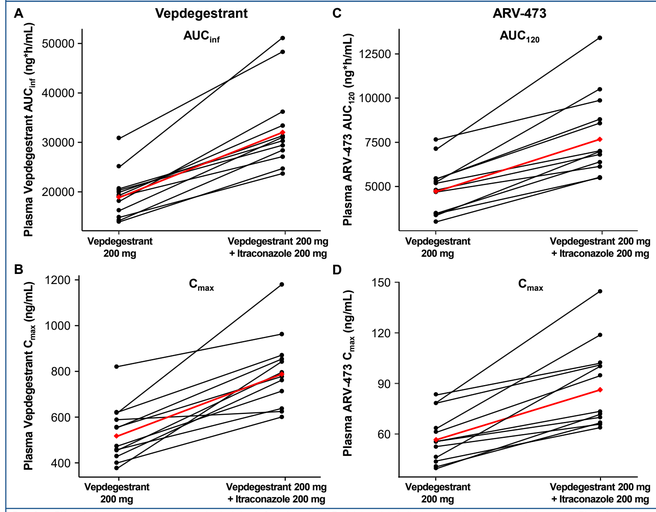
Data from PK analysis set: participants who received ≥1 dose of the study drug and had sufficient concentration-time data to reliably determine PK parameters
PK=pharmacokinetics

Table 2: Descriptive summary of plasma vepdegestrant PK parameters

PK parameter, unit	n	Vepdegestrant 200 mg reference	n	Vepdegestrant 200 mg + 11 days of itraconazole 200 mg test	Ratio of adjusted geometric means (90% CI) test/reference
Vepdegestrant					
AUC_{inf}, ng*h/mL	12	18,960 (23)	12	32,020 (24)	168.9 (157.7–180.9)
C_{max}, ng/mL	12	517.9 (22)	12	788.2 (19)	152.2 (136.9–169.2)
T_{max}, h	12	6.0 (2.0–8.0)	12	6.0 (4.0–8.0)	-
$t_{1/2}$, h	12	42.6 ±4.08	12	61.6 ±9.12	-
CL/F, L/h	12	10.5 (23)	12	6.2 (24)	-
V_z/F, L	12	645.6 (29)	12	549.5 (20)	-
ARV-473					
AUC_{120}, ng*h/mL	12	4734 (30)	12	7668 (28)	162.0 (148.7–176.5)
C_{max}, ng/mL	12	56.4 (26)	12	86.3 (27)	153.1 (138.5–169.3)
T_{max}, h	12	24.0 (24.0–48.1)	12	35.9 (12.0–47.8)	-
$t_{1/2}$, h	2	39.1, 47.5	6	50.3 ±5.6	-

Data from PK analysis set: participants who received ≥1 dose of vepdegestrant. Data are presented as geometric mean (CV%) except for T_{max}, which is presented as median (min–max) and $t_{1/2}$, which is presented as arithmetic mean ± standard deviation; individual values are listed separated by a comma when there are <3 evaluable measurements. For AUC_{120} and C_{max} of ARV-473, manual correction was applied to account for predose residual ARV-473 concentrations in period 2 that were >5% of C_{max} due to carryover from dosing in period 1 observed in 8/12 participants
AUC_{120}=area under the concentration-time curve from time 0 to 120 hours; AUC_{inf}=area under the concentration-time curve from time 0 extrapolated to infinity; CL/F=apparent total clearance after extravascular administration; C_{max}=maximum plasma concentration; CV=coefficient of variation; PK=pharmacokinetics; $t_{1/2}$=apparent first-order terminal elimination half-life; T_{max}=time to reach C_{max}; V_z/F=apparent volume of distribution during the terminal elimination phase after extravascular administration

Figure 3: Individual and geometric mean (A) AUC_{inf} and (B) C_{max} of vepdegestrant and (C) AUC_{120} and (D) C_{max} of ARV-473 by treatment



Data from PK analysis set: participants who received ≥1 dose of vepdegestrant. Red data points indicate geometric mean for each parameter. Black data points indicate individual values. Itraconazole 200 mg was given for 11 days and a single dose of vepdegestrant 200 mg was given on day 5
AUC_{120}=area under the concentration-time curve from time 0 to 120 hours; AUC_{inf}=area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}=maximum plasma concentration; PK=pharmacokinetics

Safety

- A total of 3 TEAEs were reported in 2 (16.7%) participants following a single dose of vepdegestrant, a total of 4 TEAEs were reported in 3 (25.0%) participants following a single dose of itraconazole, and a total of 3 TEAEs were reported in 2 (16.7%) participants following a single dose of vepdegestrant with itraconazole; all were mild or moderate
- TRAEs were reported in 1 (8.3%) participant who received vepdegestrant 200 mg; both were mild (**Table 3**)
- No serious or severe AEs occurred and no discontinuations or dose modifications due to AEs were reported
- No clinically meaningful changes in vital sign, ECG, or laboratory measurements were observed

Table 3: Summary of TRAEs

AEs by preferred term, n (%)	Vepdegestrant 200 mg (N=12)	Vepdegestrant 200 mg + 11 days of itraconazole 200 mg (N=12)
Any TRAE	1 (8.3)	0
Abdominal pain	1 (8.3)	0
Diarrhea	1 (8.3)	0

Data from safety analysis set: participants who received ≥1 dose of vepdegestrant or itraconazole
AE=adverse event; TRAE=treatment-related adverse event