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Evaluating CYP3A4-Mediated Drug Interaction Risks for Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader, in Combination With Cyclin-Dependent Kinase 4/6 Inhibitors and Everolimus

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Objective

- To evaluate the effect of multiple doses of vepdegestrant (ARV-471) on the pharmacokinetics (PK) of midazolam, a sensitive cytochrome P450 (CYP)3A4 substrate index drug
- To assess the potential risk of CYP3A4-mediated drug interactions with anticancer agents currently being tested in combination with vepdegestrant, such as cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and everolimus

Key Findings

- In healthy adult females of nonchildbearing potential (N=15), coadministration of multiple doses of vepdegestrant 200 mg once daily (QD) with a single oral dose of midazolam 2 mg increased the midazolam area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinity (AUC_{inf}) by 74%
  - According to the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use M12 drug interaction guidance, vepdegestrant can be classified as a weak CYP3A4 inhibitor, which is defined by a ≥1.25- to <2-fold increase in the AUC of a sensitive index CYP substrate[1]
- Vepdegestrant 200 mg QD for 15 days was well tolerated with no new safety issues identified
- Drug-drug interaction (DDI) modeling results demonstrated that the predicted effects of vepdegestrant on combination partners (palbociclib, abemaciclib, ribociclib, and everolimus), based on CYP3A4 metabolism, are unlikely to have a major impact in clinical combinations

Conclusions

- Vepdegestrant showed a weak inhibitory effect on CYP3A4-mediated metabolism in this phase 1 study with midazolam; the study results, combined with mathematical modeling, suggest low potential of CYP3A4-mediated drug interactions for vepdegestrant in combination with CDK4/6 inhibitors and everolimus
  - Recent findings from the TACTIVE-U study reported an ~13% increase in plasma exposure of abemaciclib when dosed with vepdegestrant, confirming the low potential of DDI for this combination (see SABCS 2024 poster P4-12-03 presented by J Hilton et al)
- Additional data to evaluate vepdegestrant in combination with these anticancer therapies are anticipated from ongoing clinical studies in patients with estrogen receptor–positive (ER+)/human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer

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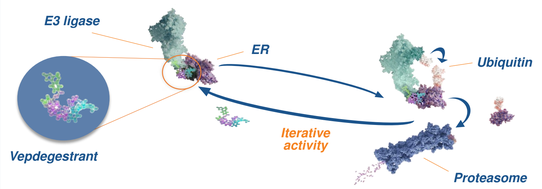
Background

- Vepdegestrant (ARV-471) is an investigational, orally administered PROTAC ER degrader that directly binds an E3 ubiquitin ligase and ER, triggering proteasomal degradation of ER[2,3] (**Figure 1**)
- In a first-in-human phase 1/2 study, vepdegestrant showed a manageable safety profile and signals of clinical efficacy as a single agent and in combination with the CDK4/6 inhibitor palbociclib in heavily pretreated patients with ER+/HER2- advanced breast cancer (NCT04072952)[4-6]
- Ongoing studies are evaluating vepdegestrant in combination with other anticancer therapies in patients with ER+/HER2- advanced breast cancer, including abemaciclib (NCT05548127) or ribociclib (NCT05573555) in the phase 1b/2 TACTIVE-U umbrella study and everolimus in the phase 1b TACTIVE-E study (NCT05501769)[7,8]
- Additionally, vepdegestrant 200 mg QD is currently being evaluated in phase 3 studies as monotherapy (VERITAC-2 [NCT05654623]) and in combination with palbociclib (VERITAC-3 [NCT05909397]) for patients with ER+/HER2- advanced breast cancer[9,10]

Figure 1: Mechanism of action of vepdegestrant[a]



Please scan this QR code with your smartphone to view **a video of the mechanism of action of vepdegestrant.**

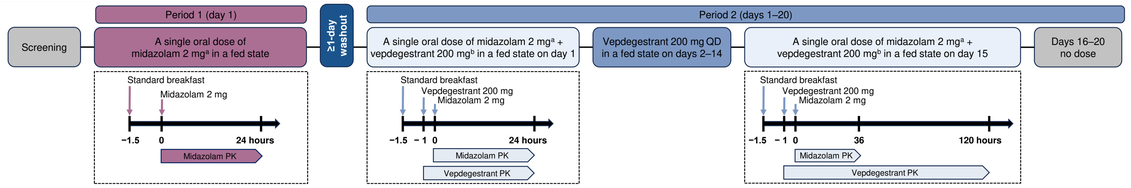
[a]General PROTAC protein degrader is shown.
ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera.

Methods

Effect of Vepdegestrant on Midazolam PK

- This phase 1, open-label, 2-period, fixed-sequence study was conducted in 15 healthy adult females of nonchildbearing potential (NCT06256510; **Figure 2**)
  - In period 1, participants received a single oral dose of midazolam 2 mg alone, followed by a ≥1-day washout period
  - In period 2, participants received vepdegestrant 200 mg QD orally under fed conditions on days 1–15, and a single oral dose of midazolam 2 mg on days 1 and 15 ~1 hour after vepdegestrant dosing
- Serial plasma samples were analyzed to estimate the effect of vepdegestrant on midazolam PK parameters using a noncompartmental approach
- Natural log–transformed PK parameters of midazolam (AUC_{inf} and maximum observed concentration [C_{max}]) were analyzed using a mixed-effects model, which included treatment as a fixed effect and participant as a random effect

Figure 2: Study design



[a]Administered as 1 mL of a 2 mg/mL oral solution.
[b]Administered orally as 2 tablets of 100 mg.
PK=pharmacokinetics; QD=once daily.

Predicting the Effect of Vepdegestrant on Combination Partners

- A static mechanistic modeling approach[11-13] was used to calculate the predicted effect of vepdegestrant 200 mg QD administration on the PK of palbociclib, abemaciclib, ribociclib, and everolimus, represented as the ratio of AUC (AUC_r) of the combination partner in the presence and absence of vepdegestrant by the following equation:

$$AUC_r = \left\{\frac{1}{A_g \times (1-F_g) + F_g}\right\} \times \left\{\frac{1}{A_h \times F_m + (1-F_m)}\right\}$$

  - A_g and A_h are the CYP3A4-mediated inhibitory effects of vepdegestrant in the gut and liver, respectively, calculated from the maximum vepdegestrant concentrations observed following 15 days of vepdegestrant 200 mg QD
  - F_g is the fraction available after intestinal metabolism; F_m is the fraction of CYP3A4-mediated hepatic clearance of the substrate that is subject to inhibition
- Static models were developed by integrating in vitro data of DDI mechanisms (as victim of CYP3A4-mediated metabolism) for each combination partner, as described in the literature[14-17]; the observed effect of vepdegestrant on midazolam AUC was used to verify the models

Results

Demographics and Baseline Characteristics

- 15 healthy female participants were enrolled and received at least 1 dose of any study intervention (**Table 1**)
  - 14 participants received and completed the study interventions as planned; 1 participant received a single dose of midazolam and did not proceed into period 2

Table 1: Demographics and baseline characteristics

Characteristic	Participants (N=15)
Sex, n (%)	
Female	15 (100)
Age, median (range), years	62 (51–74)
Race, n (%)	
White	15 (100)
Ethnicity, n (%)	
Not Hispanic or Latino	15 (100)
Weight, median (range), kg	66 (52–91)
BMI, median (range), kg/m^2	26 (22–32)

BMI=body mass index.

Pharmacokinetics

- Following midazolam administration with multiple doses of vepdegestrant (test) compared with midazolam alone (reference), the test/reference ratios of the adjusted geometric means (90% CIs) for midazolam AUC_{inf} and C_{max} were 174.4 (158.6–191.8) and 115.0 (103.5–127.8), respectively (**Table 2**)
- Following midazolam administration with a single dose of vepdegestrant (test) compared with midazolam alone (reference), the test/reference ratios of the adjusted geometric means (90% CIs) for midazolam AUC_{inf} and C_{max} were 106.3 (100.5–112.5) and 89.1 (81.1–97.9), respectively (**Table 2**)

Table 2: Plasma midazolam PK parameters in the absence and presence of vepdegestrant

Parameter	Midazolam 2 mg alone[a] reference	Single dose of vepdegestrant: Midazolam 2 mg + vepdegestrant 200 mg[a] test	Single dose of vepdegestrant: Ratio of adjusted geometric means[b] (90% CI)[b] test/reference	Multiple doses of vepdegestrant: Midazolam 2 mg + vepdegestrant 200 mg QD[a] test	Multiple doses of vepdegestrant: Ratio of adjusted geometric means[b] (90% CI)[b] test/reference
AUC_{inf}, ng*h/mL	29.2 (29)	33.3 (23)	106.3 (100.5–112.5)	51.1 (28)	174.4 (158.6–191.8)
C_{max}, ng/mL	9.0 (23)	8.1 (29)	89.1 (81.1–97.9)	10.4 (22)	115.0 (103.5–127.8)

[a]Geometric means (geometric %CV) are reported.
[b]Ratios and 90% CIs are expressed as percentages. Natural log–transformed AUC_{inf} and C_{max} for midazolam were analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect.
Data are from the PK analysis set, which includes participants who received ≥1 dose of the study drug.
AUC_{inf}=area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{max}=maximum observed concentration; CV=coefficient of variation; PK=pharmacokinetic; QD=once daily.

Safety

- Vepdegestrant 200 mg QD for 15 days was well tolerated in healthy adult female participants of nonchildbearing potential
  - No serious adverse events (AEs) or severe AEs were reported in this study, and no new safety issues were identified
- One participant experienced a non-serious AE of cystitis (moderate severity, not related to the study interventions) following the administration of a single dose of midazolam 2 mg alone and permanently discontinued from the study

DDI Prediction

- DDI modeling results demonstrated that the predicted effect of vepdegestrant on the PK of combination partners, expressed as AUC_r, ranged from 1.13–1.29 for palbociclib, 1.37–1.55 for abemaciclib, 1.00–1.04 for ribociclib, and 1.38–1.63 for everolimus (**Table 3**)
  - These predicted effects based solely on CYP3A4 metabolism are unlikely to have a major impact in clinical combinations

Table 3: In vitro data and static model–predicted effect of vepdegestrant 200 mg QD on the PK of combination partners

Drug, dose regimen	F_g[14-17]	F_m (CYP3A4)[14-17]	Calculated AUC_r
Palbociclib, 125 mg QD	0.90	0.62	1.13–1.29
Abemaciclib, 150 mg BID	0.74	0.89	1.37–1.55
Ribociclib, 600 mg QD	1.00	0.13	1.00–1.04
Everolimus, 10 mg QD	0.74	1.00	1.38–1.63

AUC_r=ratio of the area under the plasma concentration-time curve; BID=twice daily; CYP=cytochrome P450; F_g=fraction available after intestinal metabolism; F_m=fraction of CYP3A4-mediated hepatic clearance of the substrate that is subject to inhibition; PK=pharmacokinetics; QD=once daily.