Poster PII-158

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

Derek Z Yang[1], Jennifer A Winton[2], Kyle T Matschke[3], Constantino Kantaridis[4], Kimberly C Lee[2], Naihan Chen[5], Yuanyuan Zhang[6], Weiwei Tan[1]

[1]Pfizer Inc., San Diego, CA; [2]Pfizer Inc., Groton, CT; [3]Pfizer Inc., Collegeville, PA; [4]Pfizer Inc., Brussels, Belgium; [5]Pfizer Inc., Beijing, China; [6]Arvinas Operations, Inc., New Haven, CT

Objective

- To evaluate the impact of vepdegestrant (ARV-471) on the pharmacokinetics (PK) of dabigatran etexilate (a model substrate for P-glycoprotein [P-gp]) in healthy participants (NCT05673889)

Key Findings

- In healthy adult participants (N=24), co-administration of dabigatran (75 mg) with a single dose of vepdegestrant (200 mg) increased dabigatran plasma area under the concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}) by 98% and maximum plasma concentration (C_{max}) by 92%
- Treatment-emergent adverse events (TEAEs) occurred in 6 (25.0%) participants after dabigatran treatment alone and in 6 (25.0%) participants after dabigatran and vepdegestrant treatment
- Treatment-related adverse events (TRAEs) occurred in 3 (12.5%) participants after dabigatran treatment (diarrhea, dry skin, hot flush, and nausea; 1 [4.2%] each) and in 1 (4.2%) participant after dabigatran and vepdegestrant treatment (headache)

Conclusions

- Co-administration of vepdegestrant increased dabigatran exposure, suggesting that vepdegestrant is a P-gp inhibitor
  - In ongoing clinical trials in patients with breast cancer, caution is recommended when using vepdegestrant with sensitive substrates of P-gp
- The study treatments were well tolerated in healthy adults; 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.** Dabigatran etexilate. Prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc; 2023. **8.** FDA. M12 drug interaction studies. Accessed Mar 12, 2024. https://www.fda.gov/media/161199/download. **9.** EMA. Accessed Mar 12, 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf. **10.** Chu X, et al. *Clin Pharmacol Ther*. 2018;104(5):788-792.

Acknowledgments

We thank the volunteers who participated in this study, as well as the investigators, researchers, and coordinators who contributed to this study. This study is sponsored by Pfizer Inc. in collaboration with Arvinas Estrogen Receptor, Inc. Medical writing and editorial support were provided by James Banigan, PhD, Justine Lempart, PhD, and Melissa Austin of Apollo Medical Communications, part of Helios Global Group, and funded by Arvinas Operations, Inc.

Please scan this QR code to download a copy of the poster

Contact
Derek Z Yang; derek.yang@pfizer.com

American Society for Clinical Pharmacology & Therapeutics (ASCPT) Annual Meeting, Colorado Springs, CO, March 27–29, 2024

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 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 a P-gp inhibitor (data on file)
- Dabigatran etexilate, a direct thrombin inhibitor, is a known substrate of intestinal P-gp[7] and has been recommended as a probe substrate for intestinal P-gp by regulatory agencies[8,9]
- Dabigatran etexilate is a small-molecule prodrug with low systemic exposure that is rapidly absorbed and converted to dabigatran (active form) in the intestine and liver upon administration. Modulation of intestinal P-gp activity will affect dabigatran etexilate absorption, which is reflected in dabigatran plasma exposure[10]
- This study (NCT05673889) was conducted to estimate the effect of vepdegestrant on the PK of dabigatran, following a single oral dose of dabigatran 75 mg with and without co-administration of a single dose of vepdegestrant 200 mg in healthy adult participants

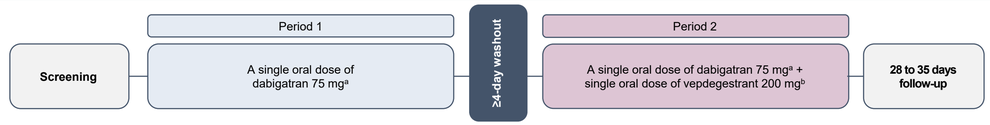
Methods

- 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 18–70 years with body mass index of 17.5–30.5 kg/m^2 and total body weight >50 kg (110 lb)
- Exclusion criteria included but were not limited to evidence or history of clinically significant conditions, active bleeding or risk of bleeding, and use of prescription or nonprescription medications within 7 days or 5 half-lives (whichever was longer) prior to the first dose of study intervention. Moderate or strong cytochrome P450 3A/P-gp 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

Figure 1: Study design



For each period, serial blood PK samples were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post dabigatran dose to determine the dabigatran PK parameters

[a]Administered as 1 capsule of 75 mg ≈2 hours after starting the standard breakfast
[b]Administered as 2 tablets of 100 mg ≈30 minutes after starting the standard breakfast
PK=pharmacokinetics

Study Design

- This was a phase 1, open-label, 2-period, fixed-sequence study in healthy adults (**Figure 1**). Participants were confined to the CRU on the day before initiating treatment until the day of clinic discharge
- Healthy participants received 2 single doses of dabigatran etexilate 75 mg. The first dose was administered alone (period 1). Following at least 4 days of washout, the second dose was administered ≈1.5 hours after a single dose of vepdegestrant 200 mg (period 2). A standard breakfast was provided in period 1 and 2

Assessment and Analyses

- Dabigatran PK parameters were estimated using a noncompartmental approach. Natural log–transformed PK parameters (C_{max} and AUC_{inf}) of dabigatran were analyzed using a mixed-effects model, which included treatments as fixed effects and participant as a random effect
- Plasma concentrations of total dabigatran (sum of unconjugated or glucuronide-conjugated dabigatran) were determined by a validated, sensitive, and specific high-performance liquid chromatography-tandem mass spectrometric method (HPLC-MS/MS) at Syneos Health (Québec, QC, Canada)
- 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 (including partial thromboplastin time [PTT]/activated PTT) were collected at screening, day −1 of period 1 (admission), and last day of each period. Prothrombin time test/international normalized ratio was collected at screening and period 1 day −1 (admission)

Results

Demographics and baseline characteristics

- Baseline characteristics of the 24 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

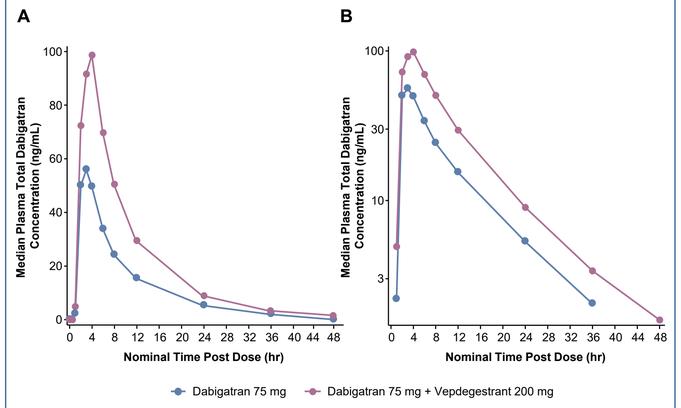
Characteristic	Total (N=24)
Age, median (range), y	43 (25–70)
Sex, n (%)	
Female	4 (16.7)
Male	20 (83.3)
Race, n (%)	
Asian	1 (4.2)
Black or African American	4 (16.7)
White	19 (79.2)
Ethnicity, n (%)	
Hispanic or Latino	2 (8.3)
Not Hispanic or Latino	22 (91.7)
BMI, median (range), kg/m^2	25.8 (21.6–30.5)
Weight, median (range), kg	78.3 (56.5–100.0)

BMI=body mass index

Pharmacokinetics

- The plasma concentration-time profiles of total dabigatran with and without vepdegestrant are presented in **Figure 2**
- Summaries of dabigatran PK parameters with and without vepdegestrant are presented in **Table 2** and displayed in **Figure 3**
  - Co-administration of dabigatran with vepdegestrant increased AUC_{inf} by 98% and C_{max} by 92%
    - Interparticipant variability in dabigatran exposure based on geometric CV% for AUC_{inf} and C_{max} were 63% and 66%, respectively, when dabigatran was co-administered with vepdegestrant, and 42% and 94%, respectively, when dabigatran was administered alone
  - Median time to reach C_{max} (T_{max}) was similar when dabigatran was administered alone and when administered with vepdegestrant
  - Apparent first-order terminal elimination half-life ($t_{1/2}$) was similar, with mean values of 9.6 hours and 9.9 hours for dabigatran alone and dabigatran with vepdegestrant, respectively

Figure 2: Median plasma total dabigatran concentrations vs time on a (A) linear and (B) semi-log scale



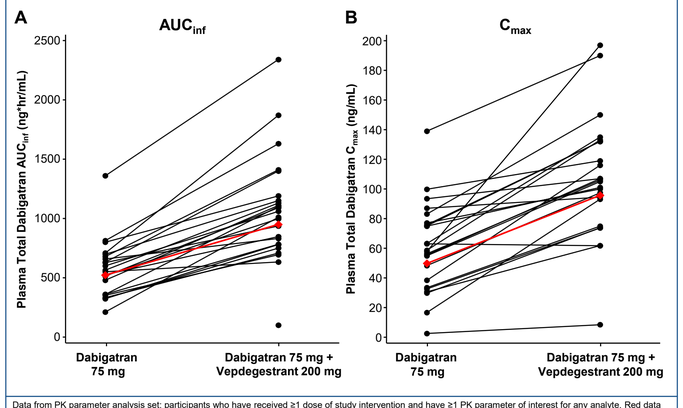
Data from PK parameter analysis set: participants who have received ≥1 dose of study intervention and have ≥1 PK parameter of interest for any analyte
PK=pharmacokinetics

Table 2: Descriptive summary of plasma total dabigatran PK parameters

PK parameter, unit	n	Dabigatran 75 mg reference	n	Dabigatran 75 mg + vepdegestrant 200 mg test	Ratio of adjusted geometric means (90% CI) test/reference
AUC_{inf}, ng*h/mL	23	522.3 (42)	24	949.6 (63)	197.8 (177.3–220.7)
C_{max}, ng/mL	24	49.8 (94)	24	95.7 (66)	192.2 (166.6–221.8)
T_{max}, h	24	3.0 (2.0–4.0)	24	3.0 (2.0–6.0)	-
$t_{1/2}$, h	23	9.6 ±1.7	24	9.9 ±1.2	-
CL/F, L/h	23	143.6 (42)	24	79.0 (63)	-
V_z/F, L	23	1956 (40)	24	1116 (58)	-

Data from PK parameter analysis set: participants who have received ≥1 dose of study intervention and have ≥1 PK parameter of interest for any analyte. 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. AUC_{inf}, $t_{1/2}$, CL/F, and V_z/F for one participant (n=1) could not be determined due to a lack of a well-characterized terminal phase.
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 plasma total dabigatran by treatment



Data from PK parameter analysis set: participants who have received ≥1 dose of study intervention and have ≥1 PK parameter of interest for any analyte. Red data points indicate geometric mean for each parameter. Black data points indicate individual values
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 9 TEAEs were reported in 6 (25.0%) participants following a single dose of dabigatran, and a total of 7 TEAEs were reported in 6 (25.0%) participants following a single dose of dabigatran and vepdegestrant
- TRAEs were reported in 3 (12.5%) participants who received dabigatran 75 mg alone and 1 (4.2%) participant who received dabigatran 75 mg with vepdegestrant 200 mg; all were mild or moderate (**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 (%)	Dabigatran 75 mg (N=24)	Dabigatran 75 mg + vepdegestrant 200 mg (N=24)
Any TRAE	3 (12.5)	1 (4.2)
Diarrhea	1 (4.2)	0
Dry skin	1 (4.2)	0
Hot flush	1 (4.2)	0
Nausea	1 (4.2)	0
Headache	0	1 (4.2)

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