W-027

Population Pharmacokinetic Model to Characterize Pharmacokinetics of Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader, in Healthy Adult Participants

Stefanie Kathrin Drescher[1]*, Derek Zhiye Yang[1]*, Eric Masson[2], Weiwei Tan[1]

*First authors contributed equally

[1]Pfizer, Inc., San Diego, CA, USA; [2]Arvinas Operations, Inc., New Haven, CT, USA

Objective

- To better understand the absorption and disposition processes of vepdegestrant, this work aimed to develop a population pharmacokinetic (PopPK) model, leveraging data obtained from several phase 1 drug-drug interactions (DDI) studies to characterize the pharmacokinetics (PK) of vepdegestrant following a single oral 200 mg dose

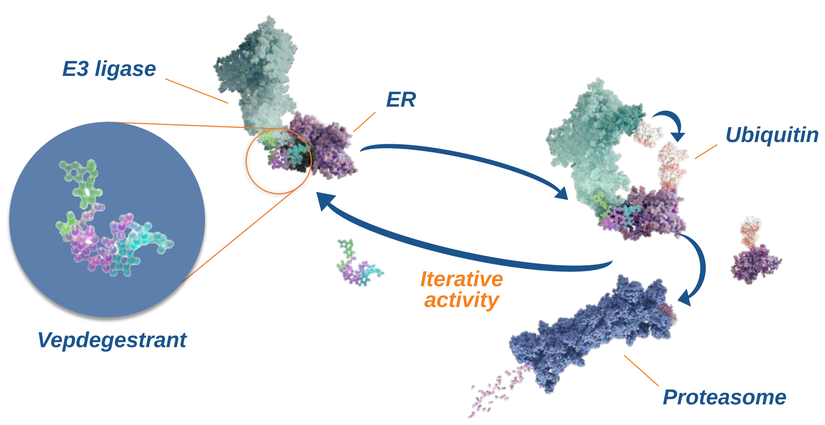
Conclusions

- The PopPK model adequately described the plasma concentrations of vepdegestrant observed in healthy participants after administration of a single oral 200 mg dose
- This model will be utilized for the development of PopPK models in patients with estrogen receptor–positive (ER+)/human epidermal growth factor receptor 2–negative (HER2-) advanced or metastatic breast cancer receiving vepdegestrant

Background

- Vepdegestrant (ARV-471; PF-07850327) is an investigational, selective, orally administered PROTAC ER degrader that directly binds an E3 ubiquitin ligase and ER, triggering proteasomal degradation of ER (**Figure 1**)[1]
- In a first-in-human phase 1/2 study (NCT04072952), vepdegestrant monotherapy was well tolerated and showed encouraging clinical activity in patients with ER+/HER2- advanced or metastatic breast cancer[2-4]
- Vepdegestrant 200 mg once daily is currently under clinical development in phase 3 studies as a monotherapy (VERITAC-2 [NCT05654623]) and in combination with palbociclib (VERITAC-3 [NCT05909397]) for patients with ER+/HER2- advanced or metastatic breast cancer[5]
- Several phase 1 clinical pharmacology studies were conducted in healthy volunteers to evaluate potential DDIs with vepdegestrant[6-8]
- Here, we present the developed PopPK model of vepdegestrant 200 mg based on these DDI studies

Figure 1: Mechanism of action of vepdegestrant[a]



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

Methods

- Participants who received a single oral dose of vepdegestrant 200 mg alone in the following phase 1 clinical pharmacology studies were included in this analysis:
  - DDI study with the P-glycoprotein substrate dabigatran (C4891008; NCT05673889)
  - DDI study with the cytochrome P450 (CYP)3A inhibitor itraconazole (C4891009; NCT05538312)
  - DDI study with the CYP3A inducer carbamazepine (C4891011; NCT06005688)
  - DDI study with the breast cancer resistance protein substrate rosuvastatin (C4891029; NCT05652660)
- Serial PK samples up to 144 hours postdose were collected, and a total of 610 vepdegestrant plasma concentrations from 60 participants were pooled for analysis
- NONMEM version 7.5.3 was used for non-linear mixed effects modeling; Perl-speaks-NONMEM (PsN) version 5.3.0 was used for visual predictive checks; and R version 4.2.1 was used for data processing
- Different absorption models, including zero-order, first-order, transit, parallel zero- and first-order, and sequential zero-order followed by first-order models, with and without lag time, were evaluated
- Demographic factors (race, age, ethnicity, and sex) were screened for potential covariates via step-wise covariate analysis
- Model performance was assessed by changes in objective functions value, parameter estimates, goodness-of-fit plots, and visual predictive check

Results

Demographics and Baseline Characteristics

- Baseline characteristics of the 60 healthy adult participants included in the PopPK analysis are shown in **Table 1**

Table 1: Demographics and baseline characteristics from the PopPK analysis dataset

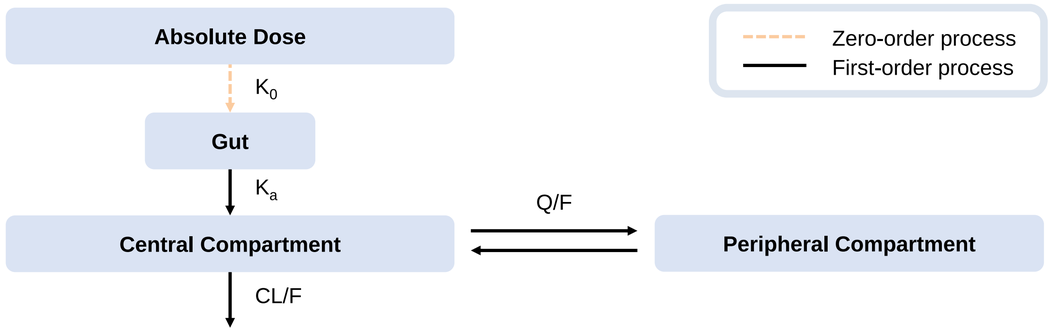
Characteristic	Total (N=60)
Age, median (range), y	44.5 (22–70)
Sex, n (%)	
Male	52 (87)
Female	8 (13)
Race, n (%)	
White	44 (73)
Black or African American	11 (18)
Asian	4 (7)
Not reported	1 (2)
Ethnicity, n (%)	
Not Hispanic or Latino	52 (87)
Hispanic or Latino	8 (13)
Weight, median (range), kg	77.8 (55.3–114.6)

PopPK=population pharmacokinetics.

PopPK Analysis

- An absorption model with sequential zero-order followed by first-order oral absorption with a lag time best described the single-dose PK profile of vepdegestrant 200 mg in healthy adults (**Figure 2**)
- The PopPK of vepdegestrant was characterized by a two-compartment model with allometric scaling of body weight (70 kg) incorporated for the parameters of apparent clearance and volume of distribution raised to a fixed exponent of 0.75 and 1, respectively
- Vepdegestrant concentrations that were below the limit of quantification represented <10% of the dataset and were not included in the analysis
- No demographic factors in this population showed any impact on the variability of PK parameters at a significance level of α=0.05
- Model evaluation indicated that the developed PopPK model was adequate and robust with good precision based on PK parameter estimates (**Table 2**) and goodness of fit plots (**Figures 3 and 4**)

Figure 2: PopPK model structure



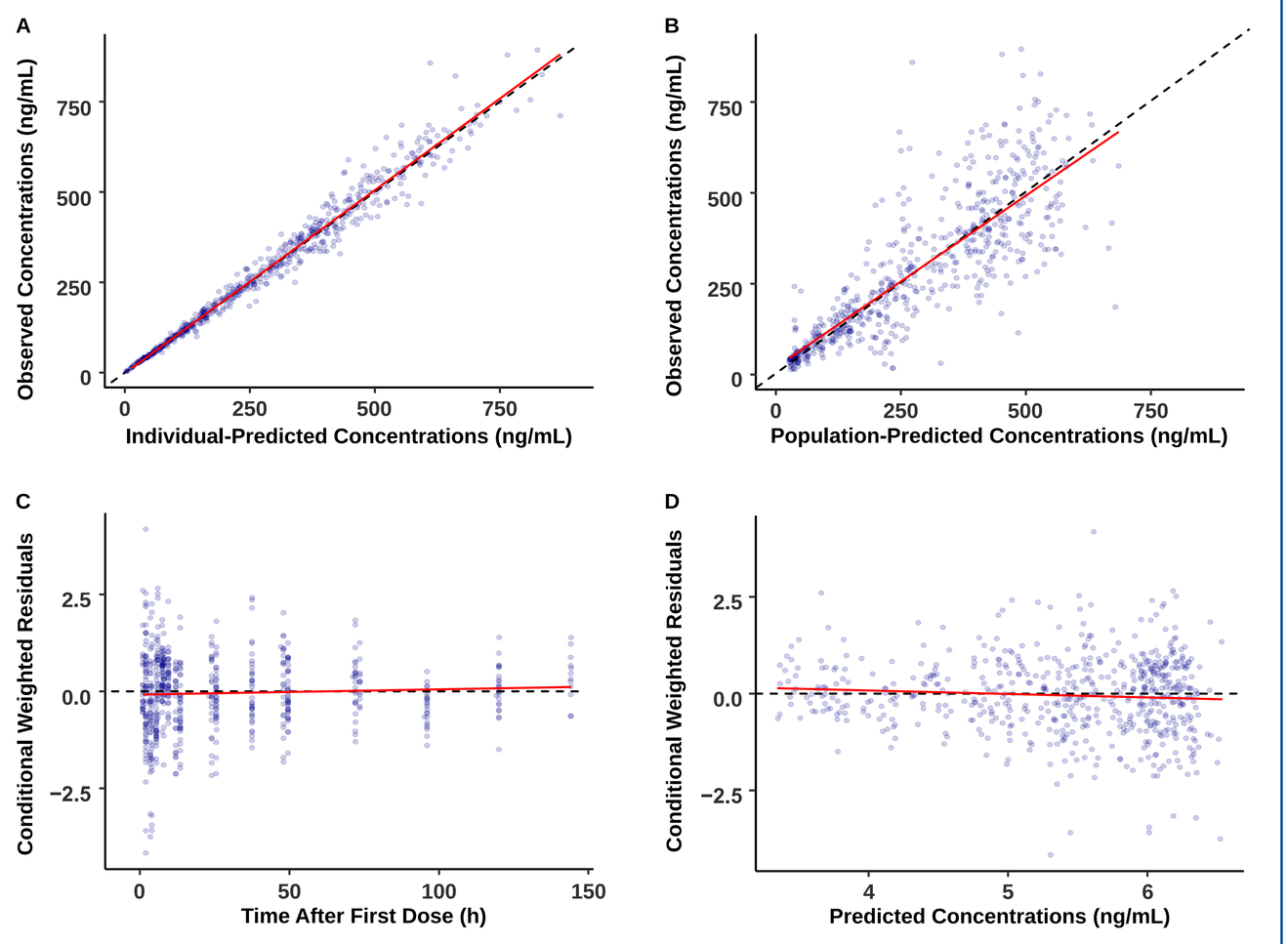
Two-compartment body model with sequential zero- and first-order absorption.
CL/F=apparent oral clearance; K_0=zero-order absorption rate constant; K_a=first-order absorption rate constant; PopPK=population pharmacokinetic; Q/F=apparent intercompartmental clearance.

Table 2: Parameter estimates for the PopPK model

Parameter	Estimate	SE	RSE%
CL/F (L/h)	8.58	0.687	8.01
V_c/F (L)	315	24.5	7.78
Q/F (L/h)	5.39	0.560	10.4
V_p/F (L)	169	10.7	6.33
K_a (1/h)	1.30	0.252	19.3
K_0 (mg/h)	103	3.29	3.19
ALAG (h)	0.522	0.0642	12.3
Proportional error	0.102	0.00371	3.64
Parameter	**Estimate**	**SE**	**CV%**
CL/F ω^2	0.0839	0.0229	29.0
V_c/F ω^2	0.0729	0.0281	27.0
K_a ω^2	0.831	0.458	91.2
K_a and ALAG covariance	−0.211	0.123	45.9
ALAG ω^2	0.453	0.151	67.3

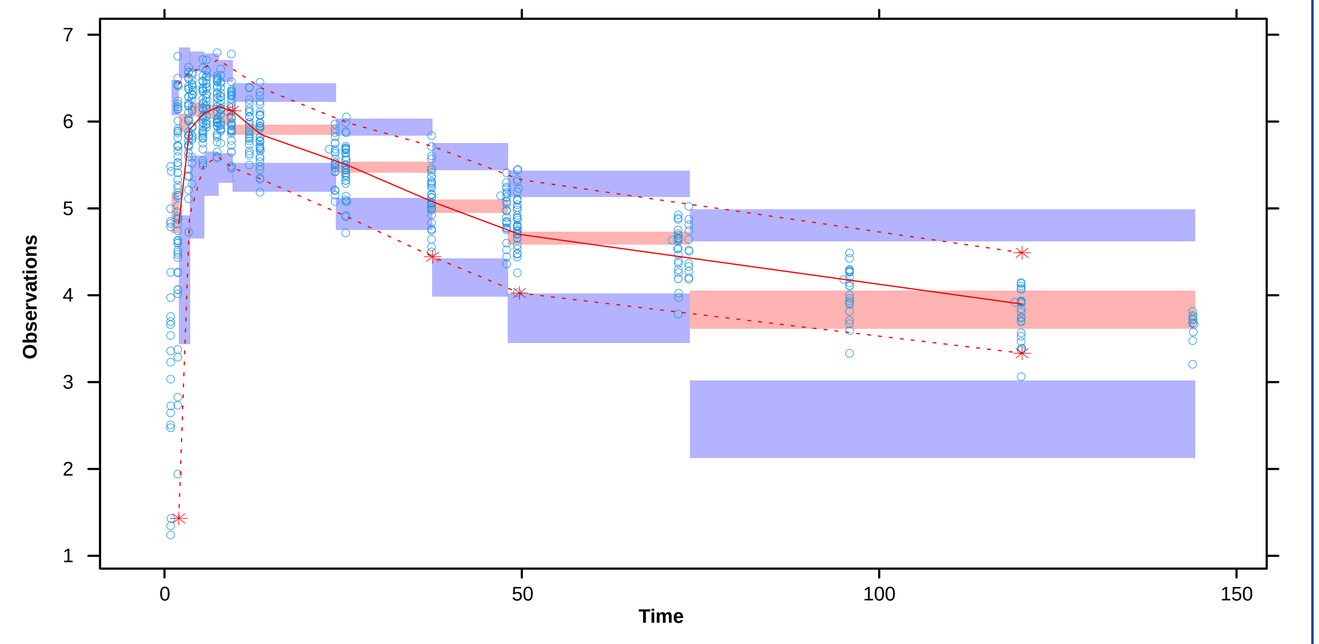
The shrinkage of individual CL/F, V_c/F, K_a, and ALAG was 1.0%, 2.4%, 12%, and 13%, respectively.
ALAG=absorption lag time; CL/F=apparent oral clearance; K_0=zero-order absorption rate constant; K_a=first-order absorption rate constant; PopPK=population pharmacokinetic; Q/F=apparent intercompartmental clearance; RSE=relative standard error; SE=standard error; V_c/F=apparent volume of distribution of central compartment; V_p/F=apparent volume of distribution of peripheral compartment.

Figure 3: Diagnostic plots for the PopPK model



Plots of (A) observed vs predicted individual vepdegestrant plasma concentrations and (B) observed vs predicted population vepdegestrant plasma concentrations. The black dashed line represents unity, and the red solid line represents linear smooth.
Plots of (C) conditional residuals vs time after first dose and (D) conditional residuals vs population predicted vepdegestrant plasma concentrations. The black dashed line represents conditional residual values of 0, and the red solid line represents linear smooth.
PopPK=population pharmacokinetic.

Figure 4: Visual predictive check of the PopPK model



Red asterisks (*) represent discrepancies between model simulations and observations. Blue open circles represent the observed vepdegestrant plasma concentrations. The red solid line represents observed median of vepdegestrant plasma concentrations. Dashed red lines represent the 2.5th and 97.5th percentile of the observed vepdegestrant plasma concentrations. Blue shading represents the 95% CI for the simulated 2.5th and 97.5th percentile. Red shading represents the 95% CI of the simulated median lines.
PopPK=population pharmacokinetic.

References

1. Gough SM, et al. Clin Cancer Res. 2024;30(16):3549-63.
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. Hamilton, EP, et al. Future Oncology. 2024:1-9. https://doi.org/10.1080/14796694.2024.2377530.
6. Yang DZ, et al. Presented at ASCPT; Mar 27–29,2024; Colorado Springs, CO. Poster PII-158.
7. Zhou L, et al. Presented at ASCPT; Mar 27–29,2024; Colorado Springs, CO. Poster PII-115.
8. Tran L, et al. Presented at ASCPT; Mar 27–29,2024; Colorado Springs, CO. Poster PII-157.

Acknowledgments

We thank the volunteers who participated in the DDI studies, as well as the investigators, researchers, and coordinators who contributed to the studies. The DDI studies were sponsored by Pfizer, Inc., in collaboration with Arvinas Estrogen Receptor, Inc. Medical writing and editorial support was provided by Genevieve R. Curtis, PhD, of Red Nucleus, and was funded by Arvinas Operations, Inc.

Contact

Stefanie Kathrin Drescher; stefanie.drescher@pfizer.com

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

American Conference on Pharmacometrics (ACoP) 15th Annual Meeting; Phoenix, AZ, USA; November 10–13, 2024