Poster: P109

ABSORPTION, METABOLISM, EXCRETION, AND PHARMACOKINETICS OF [^{14}C]VEPDEGESTRANT IN HEALTHY ADULT PARTICIPANTS

Theodore R. Johnson[1], Lana Tran[2], Jonathan N. Bauman[3], Jennifer A. Winton[4], Kyle T. Matschke[5], Craig Boyle[6], Kimberly C. Lee[7], Yuanyuan Zhang[8], and Weiwei Tan[2]

[1]Pharmacokinetics, Dynamics and Metabolism, Pfizer, Inc., San Diego, CA; [2]Clinical Pharmacology, Pfizer, Inc., San Diego, CA; [3]Pharmacokinetics, Dynamics and Metabolism, Pfizer, Inc., Groton, CT; [4]Pharmacometrics, Pfizer, Inc., Groton, CT; [5]Statistics, Pfizer, Inc., Collegeville, PA; [6]Phase I Clinic, PPD, Austin, TX; [7]Clinical Bioanalytics, Pfizer, Inc., Groton, CT; [8]Clinical Pharmacology, Arvinas Operations, Inc., New Haven, CT

Objective

- The objective of this study was to characterize the mass balance, metabolic disposition, and pharmacokinetics of vepdegestrant labeled with radioactive carbon (^{14}C) in healthy adult participants

Key Findings & Conclusions

- Vepdegestrant was well absorbed in healthy adult participants receiving a single 200 mg oral dose of [^{14}C]vepdegestrant
- Urinary excretion of vepdegestrant-related radioactivity was minimal; the vast majority of the dose was recovered in feces
- Vepdegestrant elimination is attributed to hepatic and/or intestinal metabolism, with direct sulfation and oxidation identified as the primary metabolic pathways
- The only circulating metabolite estimated to account for >10% of total drug-related material was ARV-473, the epimer of vepdegestrant
- Vepdegestrant was well tolerated in healthy adult participants, with no new safety signals identified

Background

- Vepdegestrant (ARV-471) is a potent, selective, orally bioavailable PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader[1]
- In the pivotal phase 3, open-label, randomized VERITAC-2 trial (NCT05654623), vepdegestrant was associated with significantly longer progression-free survival than fulvestrant in patients with ER-positive/human epidermal growth factor 2–negative, estrogen receptor 1 gene (*ESR1*)-mutated advanced or metastatic breast cancer who had previously received treated with endocrine-based therapy[1,2]
- In vitro metabolism studies indicated that oxidative *N*-dealkylation of vepdegestrant results in intramolecular cleavage, suggesting that this metabolic pathway could occur in humans (**Figure 1**)
- Separate radiolabeled forms of vepdegestrant were therefore synthesized to enable characterization of the disposition of both the selective ER modulator (phenyl-^{14}C) and cereblon (oxoisoindolin-^{14}C) moieties of vepdegestrant (**Figure 1**)

Methods

Study Design

- In this open-label, 2-arm, parallel study, 12 healthy adult males and females of non-childbearing potential received a single oral dose of [^{14}C]vepdegestrant (200 mg/100 µCi), formulated as an oral suspension, under fed conditions
- Participants were randomized to receive [phenyl-^{14}C]vepdegestrant (3 males/3 females) or [oxoisoindolin-^{14}C]vepdegestrant (2 males/4 females)
- Blood (for plasma), urine, and feces were collected predose and at various intervals up to 408 h postdose for pharmacokinetics (PK), mass balance, and clinical laboratory assessments
- Adverse events (AEs) were monitored throughout the study

Analyses

Determination of Total Radioactivity

- Total radioactivity (TRA) in plasma and urine was determined directly by liquid scintillation counting (LSC)
- Fecal samples were combusted prior to analysis by LSC
- The lower limit of quantitation (LLOQ) of TRA in plasma was 91.5 ng-eq/mL

Quantification of Vepdegestrant & ARV-473 in Plasma

- The concentration of vepdegestrant and its inactive (ER degradation) epimer ARV-473 (**Figure 2A**) in plasma was determined by a validated liquid chromatography–mass spectrometry method using a chiral chromatography column to achieve separation
- The LLOQ for both analytes in plasma was 2.50 ng/mL

Pharmacokinetic Analysis

- PK parameters for vepdegestrant, ARV-473, and TRA in plasma were calculated using standard noncompartmental methods

Metabolite Profiling

- For profiling plasma and feces, samples were pooled according to treatment arm and participant sex, with the resultant composite samples representing >90% of plasma TRA AUC and recovered dose, respectively
- Urine samples were not profiled, as <3% of the dose was excreted in urine
- Metabolite profiles of extracted samples (protein precipitation) were generated using reversed-phase HPLC with fraction collection followed by LSC
- Metabolites were identified using an in-line hybrid quadrupole time-of-flight tandem mass spectrometer
- The profiling method did not chromatographically resolve vepdegestrant from ARV-473; therefore, the reported abundance values for unchanged vepdegestrant represent the sum of both analytes, and the reported metabolites correspond to products of either epimer

Figure 1. Structures of radiolabeled forms of [^{14}C]vepdegestrant

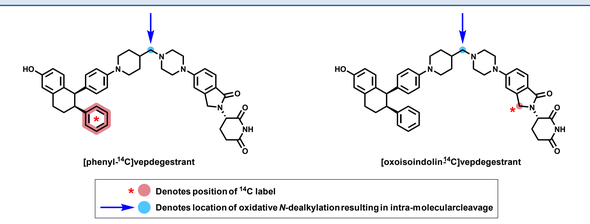
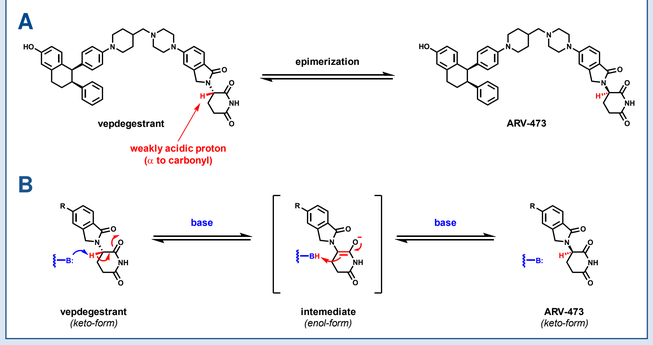


Figure 2. (A) Structures of vepdegestrant and its epimer ARV-473 and (B) proposed mechanism of epimerization/chiral inversion



Results

Participant Demographics

- The majority of the 12 participants enrolled in this study were White (75%)
- The mean (SD) age was 52.8 (13.4) years, and the mean (SD) body weight was 73.4 (13.0) kg
- Demographics between treatment groups were generally similar
- One participant administered [oxoisoindolin-^{14}C]vepdegestrant withdrew from the study early, resulting in incomplete collection of excreta samples, and was excluded from subsequent PK/ADME analyses

Safety

- Treatment-emergent AEs occurred in 1 (17%) participant receiving [phenyl-^{14}C]vepdegestrant and 3 (50%) participants receiving [oxoisoindolin-^{14}C]vepdegestrant
  - The most common treatment-emergent AEs among all participants were diarrhea (n=2) and infrequent bowel movements (n=2)
- All reported AEs were mild, and none were treatment related

Excretion and Mass Balance

- Following administration of [phenyl-^{14}C]vepdegestrant, the mean total recovery of the dose was 69.2% (n=6), with 0.5% and 68.6% recovered in urine and feces, respectively (**Figure 3A**)
- Following administration of [oxoisoindolin-^{14}C]vepdegestrant, the mean total recovery was 70.1% (n=5), with 2.6% and 67.5% recovered in urine and feces, respectively (**Figure 3B**)
- Due to suboptimal recovery across study participants, potential causes were investigated:
  - Dose accuracy was confirmed
  - PK parameters for vepdegestrant and ARV-473 were consistent with historical values
  - In rats, total recovery was ~100%, suggesting that radiolabel positions were metabolically-stable
  - There was no evidence of covalent binding of vepdegestrant-related radioactivity to tissue or blood proteins
- Although the reason for incomplete recovery is unknown, this finding was not deemed to impact the overall integrity of the study, as:
  - Recovery fell within the range reported for drugs approved by FDA over the past 2 decades[3]
  - Low recovery alone does not compromise the study if all major objectives are achieved[4,5]

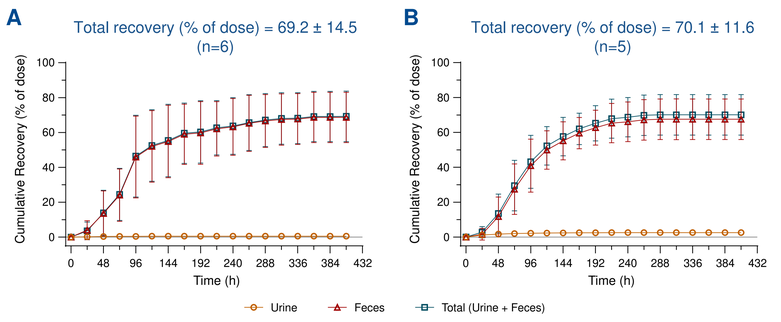
Plasma Pharmacokinetics

- PK of vepdegestrant, ARV-473, and TRA were similar in both treatment arms (**Figure 4; Table 1**)
- Vepdegestrant reached maximum plasma concentrations within 6 h, with a mean terminal half-life ($t_{1/2,z}$) of ~70 h
- The rate of epimerization of vepdegestrant to ARV-473 was slow; the time to reach the maximum concentration (T_{max}) of ARV-473 was ≥24 h
- Chiral inversion of vepdegestrant to ARV-473 is proposed to occur via base-catalyzed, nonenzymatic, bidirectional epimerization (**Figure 2B**)[6]
- The mean molar ratio of ARV-473 to vepdegestrant for AUC_{inf} was ~32%, and the $t_{1/2,z}$ of ARV-473 was similar to that of vepdegestrant, collectively suggesting that ARV-473 displays typical formation rate-limited metabolite elimination kinetics
- Combined, vepdegestrant and ARV-473 represented ~50% of drug-related material in plasma (AUC_{inf})
- TRA concentrations declined in parallel with vepdegestrant and ARV-473 (**Figure 4**), suggesting that vepdegestrant-related radioactivity does not covalently bind to blood proteins

Metabolite Profiling

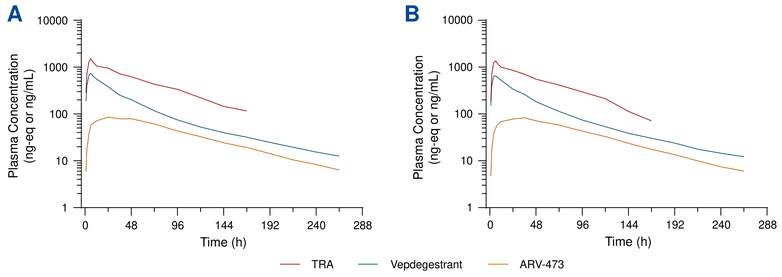
- Metabolite profiles were consistent between the [^{14}C]vepdegestrant treatment arms and sexes
- The major circulating drug-related component in plasma was unchanged total vepdegestrant (vepdegestrant + ARV-473), accounting for ~92% of plasma radioactivity (**Figure 5A; Table 2**)
- Individually, vepdegestrant and ARV-473 were estimated to account for ~69% and ~23% of circulating radioactivity, respectively
- The *O*-sulfate (M4) and the co-eluting *O*-glucuronide (M1) / hydroxy-*O*-glucuronide (*m/z* 916) metabolites were minor components in circulation, individually accounting for ≤5% of plasma radioactivity (**Figure 6; Table 2**)
- The difference in the percentage of circulating radioactivity attributed to total vepdegestrant between the plasma PK (~50%; **Table 1**) and profiling methods (~92%; **Table 2**) was attributed to the incomplete extraction of TRA from the plasma profiling samples (68%–77%)
- The major drug-related components excreted in feces were the *O*-sulfate conjugate (M4) and unchanged vepdegestrant, accounting for ~36% and ~18% of the dose, respectively (**Figure 5B; Table 2**)
- The remaining components in feces were comprised of numerous oxidative and hydrolytic metabolites, individually accounting for ≤5% of the dose (**Figure 6; Table 2**)
- Oral absorption of vepdegestrant was estimated to be ≥74%, assuming that unchanged vepdegestrant in feces (scaled to 100% recovery) represented unabsorbed drug

Figure 3. Mean (± SD) cumulative excretion of TRA following a single 200 mg oral dose of (A) [phenyl-^{14}C]vepdegestrant and (B) [oxoisoindolin-^{14}C]vepdegestrant



SD = standard deviation; TRA = total radioactivity.

Figure 4. Mean concentration-time profiles of TRA, vepdegestrant, and ARV-473 in plasma following a single 200 mg oral dose of (A) [phenyl-^{14}C]vepdegestrant and (B) [oxoisoindolin-^{14}C]vepdegestrant



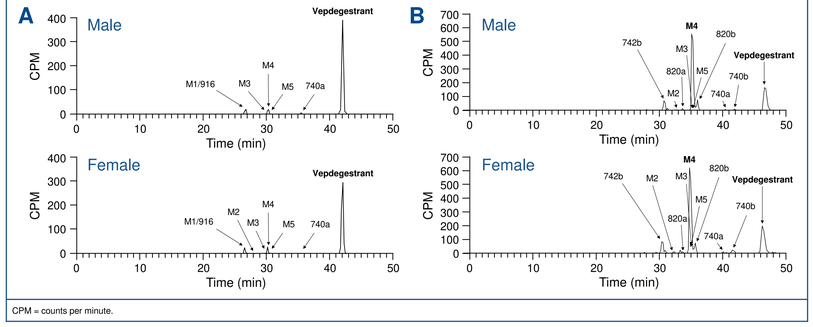
LLOQ was 91.5 ng-eq/mL for TRA and 2.50 ng/mL for both vepdegestrant and ARV-473.
LLOQ = lower limit of quantitation; TRA = total radioactivity.

Table 1. Pharmacokinetic parameters of vepdegestrant, ARV-473, and TRA in plasma following a single 200 mg oral dose of [^{14}C]vepdegestrant

	[phenyl-^{14}C]vepdegestrant (n=6)			[oxoisoindolin-^{14}C]vepdegestrant (n=5)		
Parameter	**Vepdegestrant**	**ARV-473**	**TRA**	**Vepdegestrant**	**ARV-473**	**TRA**
T_{max} (h)	6 (4–6)	24 (24–36)	6 (4–6)	6 (4–8)	36 (24–48)	6 (6–6)
C_{max} (ng or ng-eq/mL)	735 (22)	85.3 (15)	1480 (23)	641 (34)	82.6 (29)	1315 (29)
AUC_{last} (ng or ng-eq·h/mL)	30270 (10)	9644 (12)	79860 (19)	28180 (23)	9067 (24)	70140 (26)
AUC_{inf} (ng or ng-eq·h/mL)	31200 (11)	10080 (13)	89710 (19)	29150 (23)	9500 (24)	78830 (21)
$t_{1/2,z}$ (h)	72 (7)	64 (9)	57 (19)	71 (4)	63 (5)	48 (6)
CL/F (L/h)	6.4 (11)	-	2.2 (19)	6.9 (23)	-	2.5 (21)
$MRAUC_{inf}$	-	0.32 (8)	-	-	0.33 (4)	-
$RAUC_{inf}$	0.35 (15)	0.11 (17)	-	0.37 (3)	0.12 (4)	-
Vepdegestrant + ARV-473[a]	0.46		-	0.49		-

All parameters presented as geometric mean (% geometric CV) except median (range) for T_{max} and arithmetic mean (SD) for $t_{1/2,z}$. ng is used for vepdegestrant or ARV-473; ng-eq/mL is used for TRA.
[a]Values represent the $RAUC_{inf}$ for vepdegestrant + ARV-473.
AUC_{inf} = area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; CL/F = apparent clearance; C_{max} = maximum observed concentration; CV = coefficient of variation; $MRAUC_{inf}$ = metabolite (ARV-473) to parent (vepdegestrant) molar ratio for AUC_{inf}; $RAUC_{inf}$ = ratio of vepdegestrant or ARV-473 to total radioactivity for AUC_{inf}; SD = standard deviation; $t_{1/2,z}$ = terminal half-life; T_{max} = time to reach C_{max}; TRA = total radioactivity.

Figure 5. Representative radiochromatograms of (A) plasma and (B) feces following a single 200 mg oral dose of [^{14}C]vepdegestrant



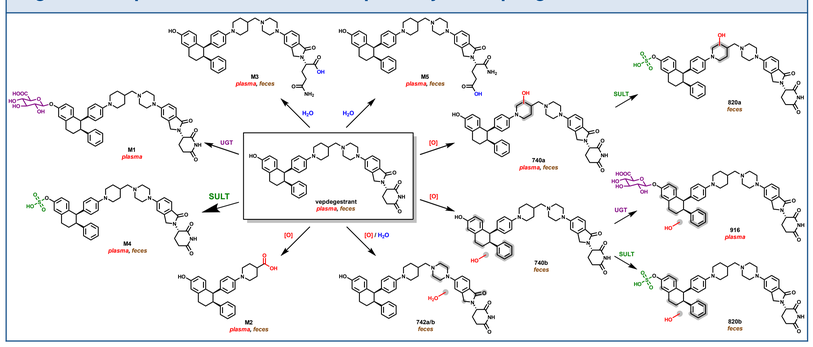
CPM = counts per minute.

Table 2. Abundance of metabolites in feces and plasma following a single 200 mg oral dose of [^{14}C]vepdegestrant

			Feces (% of dose)		Plasma (% of TRA)	
Component	***m/z* $[M+H]^+$**	**Description**	**[phenyl-^{14}C] (n=6)**	**[oxoisoindolin-^{14}C] (n=5)**	**[phenyl-^{14}C] (n=6)**	**[oxoisoindolin-^{14}C] (n=5)**
Vepdegestrant	**724**	**Parent drug**	18.4	17.5	91.0	93.7
742b	**742**	**+OH → +2H**	5.2	5.1	-	-
M1[a]	**900**	***O*-glucuronide**	-	-	4.3	2.0
M2	**428**	***N*-dealkylation**	0.4	-	0.1	-
820a	**820**	**+OH → *O*-sulfate**	0.6	0.1	-	-
M3[b]	**742**	**+H_2O (glutarimide)**	0.4	0.3	0.4	0.6
M4[b]	**804**	***O*-sulfate**	34.9	36.3	3.9	3.5
M5[b]	**742**	**+H_2O (glutarimide)**	1.5	1.4	0.3	0.3
820b	**820**	**+OH → *O*-sulfate**	3.8	4.2	-	-
740a	**740**	**+OH**	0.4	0.2	-	-
740b	**740**	**+OH**	1.0	0.3	-	-
U1 - U11	**-**	**Unidentified**	1.5	1.2	-	-
Total			68.6	67.5	100.0	100.0
***% Identified*[c]**			*96.8*	*94.7*	*100.0*	*100.0*

[a]Co-eluting with hydroxy *O*-glucuronide (*m/z* 916). [b]Co-eluting; calculated using standards. [c]In feces, calculated as: (total characterized components / total recovery in excreta) × 100.
m/z = mass-to-charge ratio; TRA = total radioactivity.

Figure 6. Proposed biotransformation pathways of vepdegestrant in humans



References

1. Campone M, et al. N Engl J Med. 2025;393(6):556-68. 2. Arvinas, Inc. August 8, 2025. Accessed August 29, 2025. https://ir.arvinas.com/news-releases/news-release-details/arvinas-announces-fda-acceptance-new-drug-application. 3. Cerny MA, et al. Drug Metab Dispos. 2023;51(6):647-56.
4. Roffey SJ, et al. Drug Metab Rev. 2007;39(1):17-43. 5. Penner N, et al. Chem Res Toxicol. 2012; 25(3):513-31. 6. Reist M, et al. Chem Res Toxicol. 1998; 11(12):1521-8.

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 Red Nucleus and funded by Arvinas Operations, Inc.

Contact

Theodore R. Johnson, Ph.D.
theodore.johnson@pfizer.com