

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

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Objective

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

Key Findings & Conclusions

- Vepdegestrant was well absorbed in healthy adult participants receiving a single 200 mg oral dose of [¹⁴C]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) degrader¹
- 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-¹⁴C) and cereblon (oxoisoindolin-¹⁴C) 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 [¹⁴C]vepdegestrant (200 mg/100 µCi), formulated as an oral suspension, under fed conditions
- Participants were randomized to receive [phenyl-¹⁴C]vepdegestrant (3 males/3 females) or [oxoisoindolin-¹⁴C]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 [¹⁴C]vepdegestrant

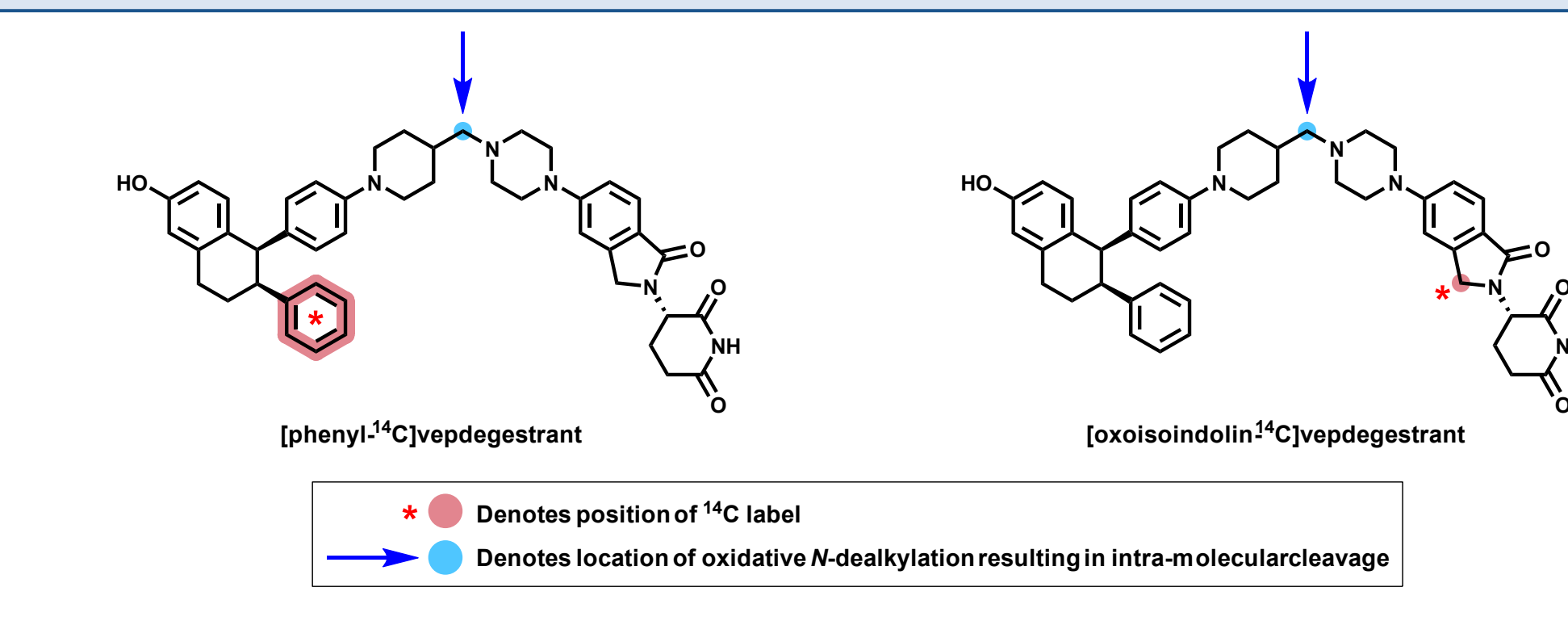
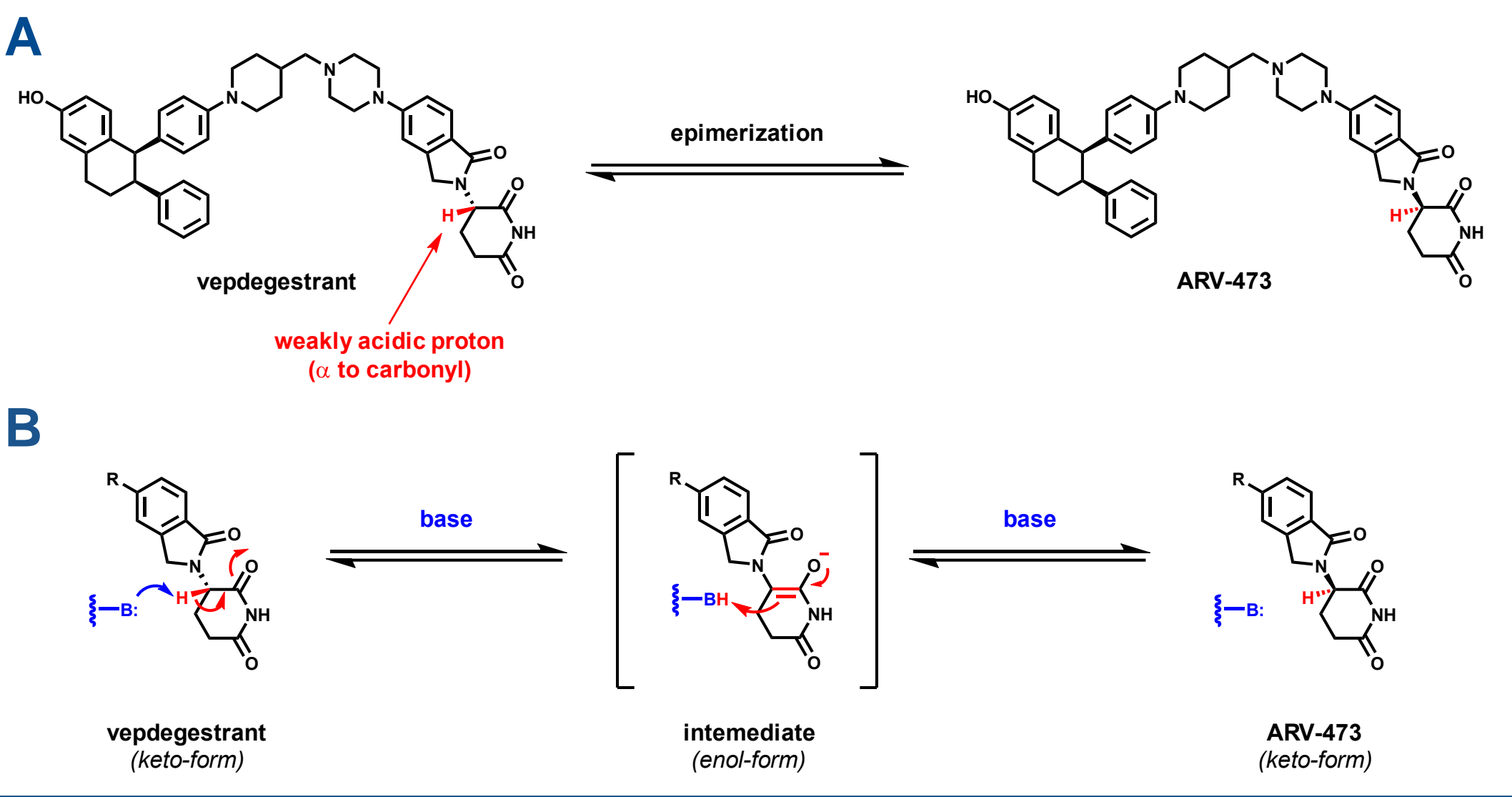


Figure 2. (A) Structures of vepdegestrant and its epimer ARV-473 and (B) proposed mechanism of epimerization/chiral inversion



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-¹⁴C]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-¹⁴C]vepdegestrant and 3 (50%) participants receiving [oxoisoindolin-¹⁴C]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-¹⁴C]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-¹⁴C]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 decades³
 - Low recovery alone does not compromise the study if all major objectives are achieved^{4,5}

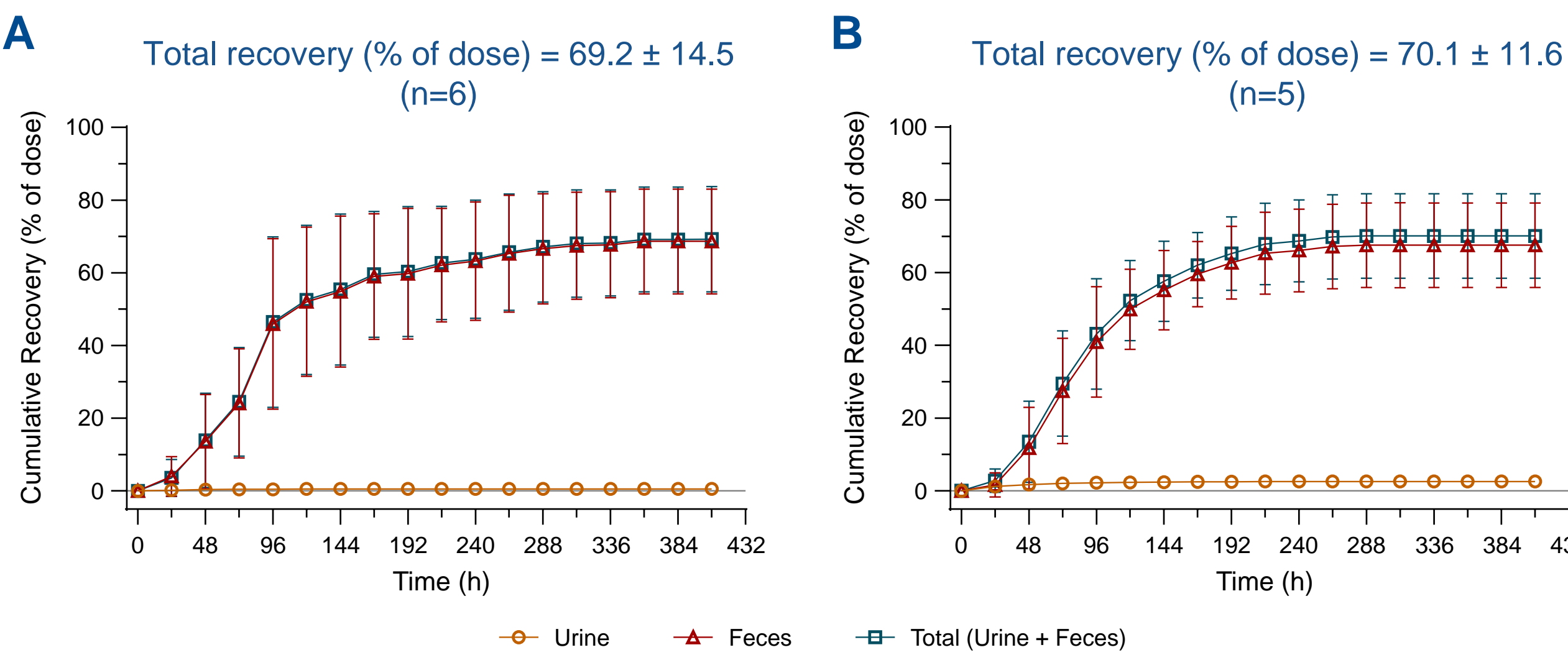
Plasma Pharmacokinetics

- 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

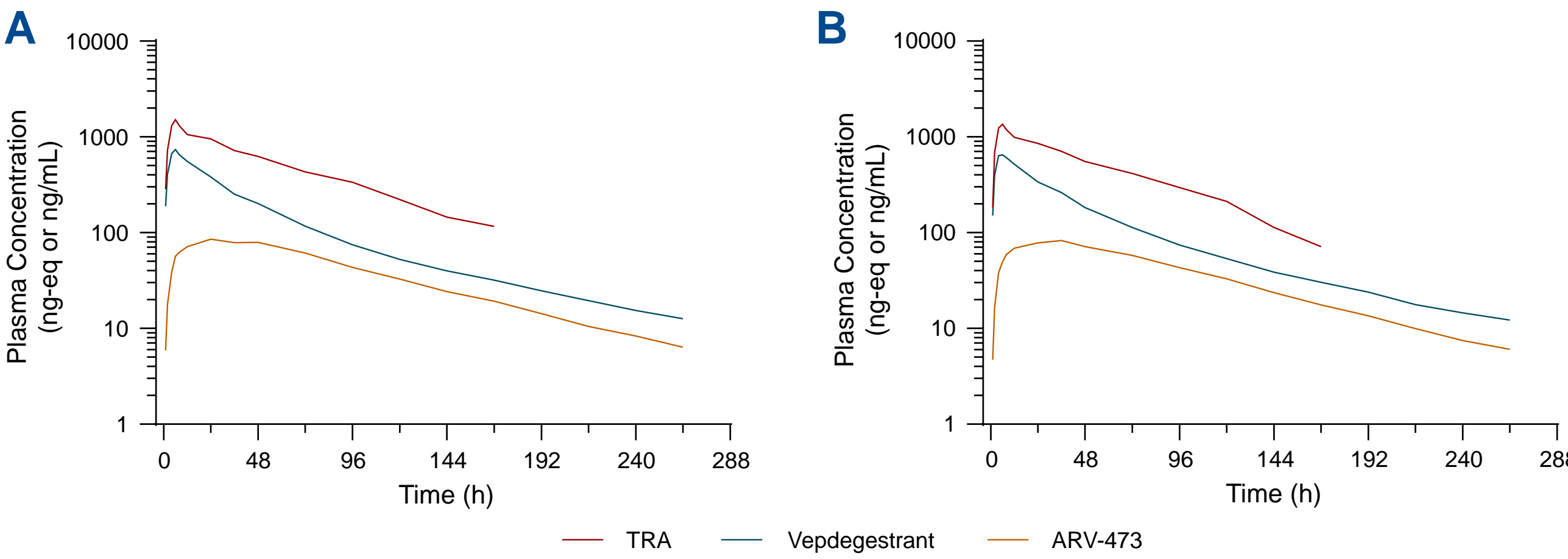
- Metabolite profiles were consistent between the [¹⁴C]vepdegestrant treatment arms and sexes
- The major circulating drug-related component in plasma was unchanged total vepdegestrant (vepdegestrant + ARV-473), accounting for ~92% of plasma radioactivity (**Figure 5A; Table 2**)
- Individually, vepdegestrant 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-¹⁴C]vepdegestrant and (B) [oxoisoindolin-¹⁴C]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-¹⁴C]vepdegestrant and (B) [oxoisoindolin-¹⁴C]vepdegestrant



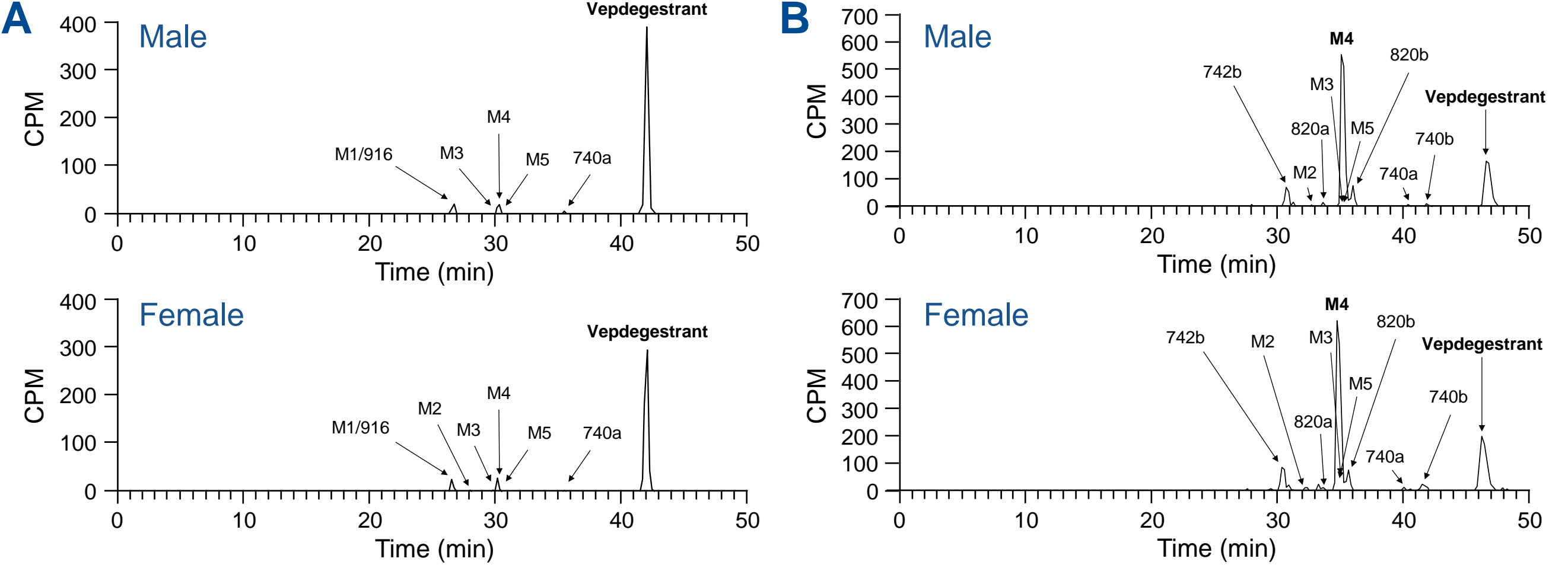
LLOQ was 91.5 ng-eq/mL for TRA and 2.50 ng/mL for both vepdegestrant and ARV-473. LLOQ = lower limit of quantitation; TRA = total radioactivity.

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

Parameter	[phenyl- ¹⁴ C]vepdegestrant (n=6)			[oxoisoindolin- ¹⁴ C]vepdegestrant (n=5)		
	Vepdegestrant	ARV-473	TRA	Vepdegestrant	ARV-473	TRA
<i>T</i> _{max} (h)	6 (4–6)	24 (24–36)	6 (4–6)	6 (4–8)	36 (24–48)	6 (6–6)
<i>C</i> _{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 (31)
<i>t</i> _{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. 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 [¹⁴C]vepdegestrant



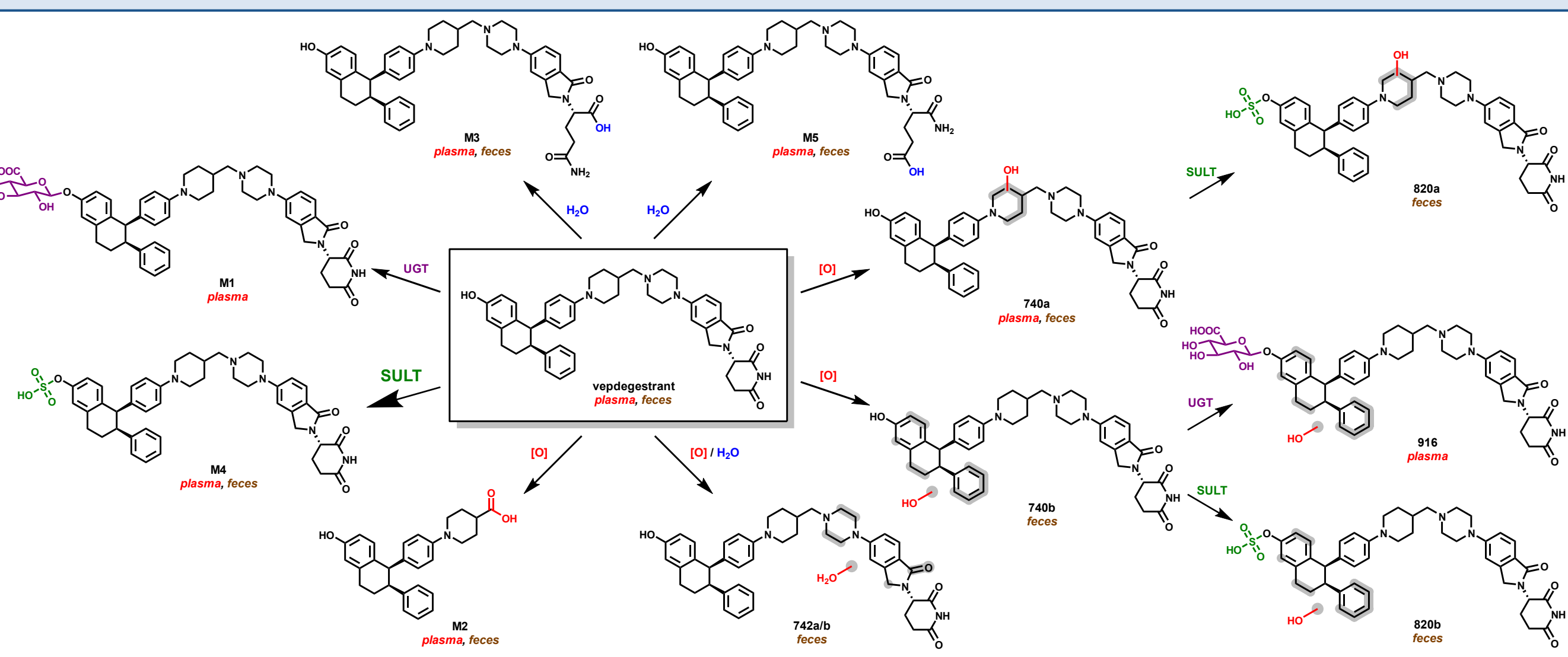
CPM = counts per minute.

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

Component	<i>m/z</i> [M+H] ⁺	Description	Feces (% of dose)		Plasma (% of TRA)	
			[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	<i>O</i> -glucuronide	-	-	4.3	2.0
M2	428	<i>N</i> -dealkylation	0.4	-	0.1	-
820a	820	+OH → <i>O</i> -sulfate	0.6	0.1	-	-
M3 ^b	742	+H ₂ O (glutarimide)	0.4	0.3	0.4	0.6
M4 ^b	804	<i>O</i> -sulfate	34.9	36.3	3.9	3.5
M5 ^b	742	+H ₂ O (glutarimide)	1.5	1.4	0.3	0.3
820b	820	+OH → <i>O</i> -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

^aCo-eluting with hydroxy *O*-glucuronides (*m/z* 916). ^bCo-eluting; calculated using standards. ^cIn feces, calculated as: (total characterized components / total recovery in excreta) × 100. ^d*m/z* = mass-to-charge ratio; TRA = total radioactivity.

Figure 6. Proposed biotransformation pathways of vepdegestrant in humans



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