Supplemental Methods.

Additional details provided including lenacapavir (LEN) structure with sites of radiolabel, experimental methods, cumulative radioactivity excretion graphs, and summary data/structures of LEN biotransformation products.

SUPPLEMENTAL DATA

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Lenacapavir Exhibits Atropisomerism - Mechanistic Pharmacokinetics and Disposition Studies of Lenacapavir Reveal Intestinal Excretion as a Major Clearance Pathway.

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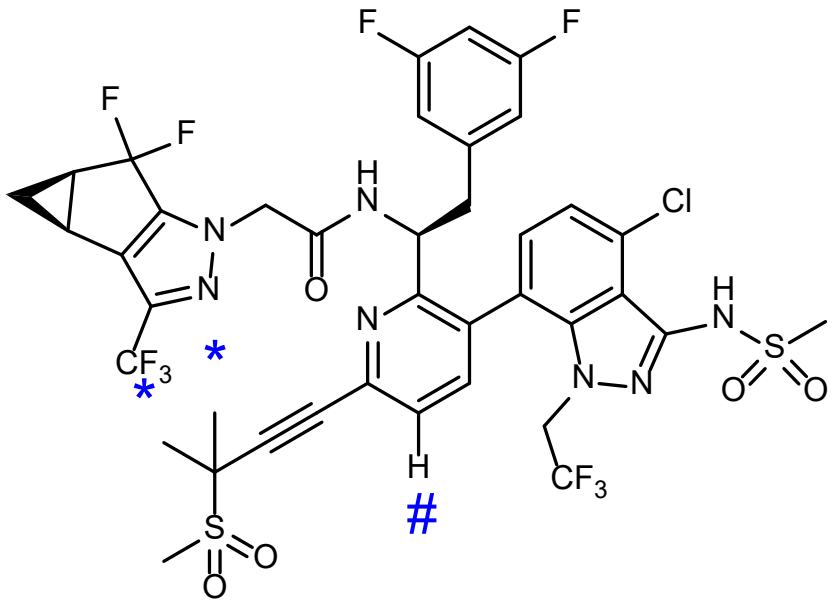
Table of contents:

SUPPLEMENTAL MATERIALS AND METHODS

Figure S1. Chemical structure of lenacapavir (LEN), [^{14}C]LEN and [^{3}H]LEN.



Radiolabel positions: * denotes ^{14}C labels in [^{14}C]LEN; # denotes ^{3}H label in [^{3}H]LEN

Permeability, Efflux, and Uptake Transporter Assessments. LEN (0.1 µM) was assessed as a substrate for efflux transporters in transwell assays using human MDR1 (P-gp-) and BCRP-transfected MDCK cell monolayers. Transporter expression-dependent changes in the bidirectional permeability assay were confirmed using control inhibitors. Cells were pre-incubated for 30 minutes prior to the assay with or without the inhibitors valspodar tested at 1 µM (P-gp) or Ko143 tested at 0.5 µM (BCRP). The experiment was started by the addition of solutions containing LEN tested at 0.1 µM or control substrates digoxin tested at 10 µM (P-gp) and cladribine tested at 10 µM (BCRP) with or without inhibitors on either apical (A to B) or basolateral (B to A) sides and incubated at 37 °C with 5% CO_2. Samples were taken at

120 minutes from the donor (apical) and receiver (basolateral) wells and analyzed in duplicate. Lucifer yellow permeability was measured at the termination of the experiment to ensure integrity of the monolayer. Permeability through a cell-free transwell was also determined as a measure of membrane passive permeability and non-specific binding. Samples were analyzed by LC-MS/MS to determine the apparent permeability and efflux ratio.

Table S1. Bi-directional permeability of LEN in human MDR1 (P-gp-) and BCRP-transfected MDCK cells

Test Article	Direction	Recovery (%)	P_{app} (10^{-6} cm/s) R1	R2	Avg.	Efflux Ratio
P-gp-transfected MDCK cells						
LEN (0.1 μM)	Cell-Free	28	2.58		2.58	
	Forward	32	0.20	0.30	0.25	35
	Reverse	25	7.62	10.1	8.85	
LEN (0.1 μM) + 1 μM Valspodar	Forward	25	5.20	4.19	4.69	1.1
	Reverse	45	3.48	6.88	5.18	
Digoxin (10 μM)	Forward	76	0.05	0.07	0.06	131
	Reverse	83	8.17	8.05	8.11	
Digoxin (10 μM) + 1 μM Valspodar	Forward	72	0.34	0.36	0.35	1.0
	Reverse	82	0.32	0.37	0.35	
BCRP-transfected MDCK cells						
LEN (0.1 μM)	Cell-Free	28	2.58		2.58	
	Forward	45	0.87	0.59	0.25	12
	Reverse	29	8.11	10.0	8.85	
LEN (0.1 μM) + 0.5 μM Ko143	Forward	38	0.63	0.97	4.69	13
	Reverse	26	8.73	11.6	5.18	
Cladribine (10 μM)	Forward	82	0.10	0.08	0.06	73
	Reverse	86	6.51	7.25	8.11	
Cladribine (10 μM) + 0.5 μM Ko143	Forward	82	0.22	0.18	0.35	0.9
	Reverse	91	0.17	0.19	0.35	

LEN was also evaluated as a potential substrate for uptake transporters organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 using Chinese hamster ovary (CHO) cells transfected with the individual transporters. The uptake rate of LEN (0.1 μM) in OATP1B1- and OATP1B3-overexpressing cells was determined in the absence or presence of the control inhibitor rifampicin (40 μM); positive control (atorvastatin) and negative control (antipyrine) substrates were also assessed. Hepatic uptake of LEN (0.025 μM) was also assayed in

cryopreserved human hepatocytes. Rosuvastatin was used as the positive control in this study and rifamycin (100 μM) was used as the inhibitor of hepatic uptake by OATP transporters.

Table S2. Uptake rates for LEN and control compounds in non-transfected CHO cells (WT) and transfected CHO cells without and with rifampicin

Uptake Rate (pmole/minute/1.0x10^6 cells)	**LEN 0.025 μM**	**Atorvastatin 0.1 μM**	**Antipyrine 10μM**
	Without Rifampicin		
CHO-WT	8.4	0.17	7.0
CHO-OATP1B1	9.8	1.25	7.1
CHO-OATP1B3	11	1.30	8.3
OATP1B1 / WT Ratio	1.2	7.4	1.0
OATP1B3 / WT Ratio	1.3	7.6	1.2
	With Rifampicin		
CHO-WT	9.7	0.16	6.7
CHO-OATP1B1	10	0.32	8.4
CHO-OATP1B3	14	0.33	7.9

In Vitro Metabolism. Metabolism of [^{14}C]LEN (10 μM) was determined following incubation (2 hours) in pooled hepatic microsomes in the presence of NADPH, UDPGA and glutathione from WH rat, beagle dog, and human. The rates of metabolism and the metabolite profiles of LEN were also assessed using Hμrel® rat, dog, and human hepatic co-cultures. Hμrel® hepatic co-cultures were incubated with [^{14}C]LEN (10 μM) for 7 days with sample collection at 0, 72 and 168 hours. Metabolite formation and identity following LC separation by offline radio-detection and simultaneous inline HRMS. Incubations were terminated by the addition of acetonitrile at designated time-points. Samples were centrifuged, the supernatants were collected and evaporated to dryness under nitrogen, and the dried samples were reconstituted with 250 μL of methanol. Following mixing and centrifugation at 1600 rpm for 5 minutes, the samples were

analyzed by LSC. The reconstituted samples were analyzed for metabolite formation and identity following LC separation by offline radio-detection and simultaneous inline HRMS.

Atropisomer Rotational Energy Assessment by ^{19}F-NMR. LEN exists as a mixture of two interconvertible atropisomers (main section, Fig. 1) that arise due to restricted rotation about the biaryl carbon-carbon bond in the molecule – denoted as LEN.1 and LEN.2. The energy barriers to rotation ($\Delta G^{\ddagger}$) for LEN.2 (major) → LEN.1 (minor) and LEN.1 (minor) → LEN.2 (major) were calculated from the rate constants (k_1 and k_2) using the Eyring equation. The rate constants were determined by assuming that the interconversion of LEN sodium atropisomers is a first-order reversible process as described below, where A represents LEN.2 and B represents LEN.1:

$$\mathbf{A} \underset{k2}{\overset{k1}{\rightleftharpoons}} \mathbf{B}$$

$$-dA/dt = k_1[A] - k_2[B]$$

After substitution, re-arrangement and integration, the following equation can be derived:

$$\ln(([A]-[A]_{eq})/([A]_0-[A]_{eq})) = -(k_1+k_2)t$$

Where, [A] = [LEN.2] / ([LEN.1] + [LEN.2]). Subscripts $[A]_0$ and $[A]_{eq}$ refer to the relative concentration of LEN.2 at t=0 and at equilibrium, respectively.

Peaks for LEN.1 and LEN.2 in the ^{19}F NMR spectra of the trifluoroethyl moiety were integrated to determine the relative concentration of LEN.2 ([A]) at each time point (main section, Fig. 2B) and a plot of $-\ln(([A]-[A]_{eq})/([A]_0-[A]_{eq}))$ vs. time was constructed (main section, Fig. 2C). The slope of this plot is equal to the sum of the rate constants (k_1+k_2).

The atropisomer ratio did not significantly change between the 7 hour and 25 hour time points in solution at 37 °C, and the ratio of $[A]_{eq}/[B]_{eq}$ was determined to be 4.43. At equilibrium, $k_1[A]_{eq} = k_2[B]_{eq}$ and since $[A]_{eq}/[B]_{eq} = 4.43$, k_1 and k_2 were calculated to be 9.63×10^{-5} s^{-1} and 4.26×10^{-4} s^{-1}, respectively. The rotational energy barriers were then calculated from the rate constants using the Eyring equation:

$$k = \frac{k_B T}{h} e^{-\frac{\Delta G‡}{RT}}$$

Where k = rate constant (k_1 or k_2), k_B = Boltzmann constant (1.381×10^{-23} J/K), T = temperature (310 K), h = Planck's constant (6.626×10^{-34} J • s) and R = gas constant (8.314 J/mol • k).

After re-arrangement:

$$\Delta G‡ = -\ln\left(\frac{kh}{k_B T}\right) RT$$

$\Delta G‡$ was calculated to be 23.87 kcal/mol for LEN.2 → LEN.1 and 22.95 kcal/mol for LEN.1 → LEN.2. The half-lives ($t_{1/2}$) for LEN.1 and LEN.2 were calculated from the rate constants k_1 and k_2 using the equation:

$$t_{1/2} = \frac{\ln(2)}{k}$$

The half-lives for LEN.1 and LEN.2 at 37 °C were determined to be 0.45 hours and 2.00 hours, respectively, in human serum containing 1.5% Kolliphor (w/v).

In Vitro Atropsiomer Stability in Plasma and Buffer LC-MS Assessments. Triplicate aliquots of plasma and phosphate-buffered saline were warmed to 37 °C and the incubations were initiated by the addition of LEN to obtain final substrate concentrations of 0.1 and 1 μM, as described above and the incubations continued at 37 °C for 24 hr. For rat plasma incubations,

sampling was performed at 0, 1, 3, 6 and 24 hr. For all other matrices sampling was performed at 0 and 24 hr. Aliquots (25 µL) of the reaction mixtures were transferred into 96-well plates. Internal standard (IS) / quality check (QC) solution in ACN (225 µL) was then immediately added, and the plates were vortexed for 10 min at 1110 rpm followed by centrifugation at 4713 × g for 20 minutes. Aliquots (150 µL) of the resulting sample supernatants were transferred into wells of fresh 96-well plates containing 150 µL of water and vortexed at 1110 rpm for two minutes. Aliquots (10 µL) were analyzed by LC-HRMS method described below. Unincubated samples, also used to assess on-instrument stability, were prepared by spiking 0.1 µM LEN working solution directly to water/ACN(1:1 v/v). One group of these samples was immediately analyzed by HRMS (time = 0) and the other group was held in the LC autosampler (4°C) for 24 hr prior to analysis. Quantification of LEN was performed by analyte peak area measured on a Thermo Scientific HRMS.

The LC Instrumentation consisted of a Thermo Scientific Transcend 1250 pump, Thermo Scientific TriPlus RS autosampler injector and cool stack The LC column was a Phenomenex Kinetex C18 100 Å HPLC column (2.6 µm particle size, 3.0 × 50 mm). Mobile phases were; A: water/acetonitrile/formic acid (94.9 : 4.9 : 0.2, v/v/v) and B: acetonitrile/water/formic acid (94.9 : 4.9 : 0.2, v/v/v). Elution was achieved, at a flow rate of 1.8 mL/minute, by linear gradients. Initial condition was 30% B at 0 min, which was increased to 70% B over 2.65 min, holding for 0.45 min at 100% B and then returning to initial conditions. The column was re-equilibrated for 1.5 min between injections. The MS instrument was a Thermo Q Exactive™ operating in positive ionization mode with mass tolerance of 5 ppm and calibrated on a weekly basis. Peak areas for LEN.1 and LEN.2, and the total LEN peak area (sum of the peak areas for LEN.1 and LEN.2) were measured by monitoring 968.1508 m/z in Thermo Xcalibur (Version 4.0).

Stabilities in plasma were determined by calculating the ratio of the peak area of LEN.1 to the total LEN peak area.

In Vivo Bioanalysis. A protein precipitation procedure was followed to prepare plasma PK samples for bioanalysis. An aliquot of 50 µL of each plasma sample was added to a clean 96 well plate followed by 200 µL of cold acetonitrile (ACN) /internal standard solution (ISTD). The contents in the 96-well plate were vortex mixed and centrifuged at 2164 g. An aliquot of 75 µL of the supernatant from each well was transferred to a clean 96-well plate and diluted with 75 µL of water. An aliquot of 20 µL of the above solution was injected to the LC-MS/MS system. The standard curve and quality control (QC) samples were prepared in blank (undosed) species plasma and samples were processed as described above.

The LC Instrumentation for plasma PK analysis consisted of a Cohesive LX-2 multiplex with two identical Agilent 1100 series binary pumps, HTS Pal autosampler from LEAP Technologies (Carrboro, NC) with a cool stack The LC column was a HyPurity C_{18} HPLC column (30 x 2.1 mm, 5 µm). Mobile phases were; A: 1% acetonitrile in 10 mM ammonium formate aqueous solution with 1% formic acid and B: 80% acetonitrile in 10 mM ammonium formate with 1% formic acid. Elution was achieved, at a flow rate of 0.5 mL/minute, by linear gradients. Initial condition (for 1.5 min) was 0% B at 0 min, which was increased to 50% B over 1 min, holding for 0.5 min at 100% B and then returning to initial conditions. The column was re-equilibrated for 1.5 min between injections. The MS instrument was a TSQ Quantum Ultra triple quadrupole mass spectrometer operating in positive ionization multiple monitoring reaction mode. The Q1 and Q3 transitions were m/z 968.1 and m/z 869.0, respectively. The typical quantification range for LEN in plasma was 1 to 5000 nM).

Rat excreta samples (bile, urine, feces; Groups 6 – 9; main section Table 1) were quantified for LEN using a LC-MS/MS method similar to plasma PK samples described above. Bile and urine samples were diluted 10-fold into blank plasma, prepared in the same manner as the plasma samples, and analyzed against a plasma calibration curve. Fecal samples were homogenized by addition of 3 equivalents (3:1) of 80:20 water: ethanol; homogenized sample was diluted 5-fold into plasma and prepared in the same manner as the plasma samples and analyzed against a plasma curve.

In Vivo Sample Preparation for Metabolite Profiling. Plasma samples were pooled by time point from intact rats (0.083, 0.25, 1, 4, 24, 72 and 168 hours) and intact dogs (0.083, 0.25, 1, 4, 24, and 72 hours after IV dosing). The samples were then further pooled by group to prepare an area under the concentration-time curve (AUC)-representative pooled sample using a time-weighted pooling method (Hop et al., 1998). The radioactivity in each pooled sample was determined by liquid scintillation counting (LSC). The pooled plasma samples were extracted with either ACN (sample:ACN, 1:3 to 4, v:v), sonicated, vortex mixed, centrifuged, and the supernatants were removed. The extraction was repeated once with ACN and once with methanol (MeOH) as previously described, and the respective supernatants were combined by extraction solvent. Duplicate aliquots were analyzed by LSC to determine extraction recoveries (to conserve radioactivity, no aliquots were taken for 0.25- and 72-hour pools from orally dosed dogs). The combined supernatants from the ACN extractions were evaporated to dryness under nitrogen and reconstituted in reverse osmosis (RO) water:MeOH, (2:1, v:v). Samples were sonicated, vortex mixed, centrifuged, and duplicate aliquots were analyzed by LSC to determine reconstitution recoveries. The reconstituted samples were analyzed by liquid chromatography-

^{14}C-high resolution mass spectrometry (LC-^{14}C-HRMS). Radioactivity in each well was determined using TopCount analysis, and radiochromatograms were generated based on radioactivity counts.

Urine samples had low radioactivity (<0.2% of dose in rats and <0.3% of dose in dogs) and were not profiled. Bile samples collected at 0-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours post-dose were pooled to generate four pooled samples (0-24, 24-48, 48-96, and 96-168), including 2.5% (96-168 hour pool only) or 5.0% of each sample by weight (equivalent percent by interval). Bile samples collected from male BDC dogs at 0-4, 4-8, 8-24, 24-48, 48-72, and 72-96 hours post-dose were pooled to generate three samples (0-8, 8 24, and 24-96 hours), including 0.25 to 2.0% (equivalent percent by interval) of each sample by weight. The radioactivity in each pooled sample was determined by LSC. The radioactivity in each pooled sample was determined by LSC. A 1-mL subsample of each pooled bile sample was centrifuged, and duplicate aliquots were analyzed by LSC to determine recoveries of radioactivity.

Feces samples collected from male intact and BDC rats at 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours postdose were pooled by group and collection interval to generate 0- to 24-, 24- to 48-, 48- to 96-, and 96- to 168-hour pooled samples, including 1.5 to 5% (equivalent percent by interval) of each sample by weight. In addition, feces samples collected from male intact rats at 168-192, 192-216, 216 240, 240-264, 264-288, 288-312, and 312-336 hours post-dose were pooled to generate a 168- 336-hour pooled sample, including 1% of each sample. A subsample (0.2 g) of each pool was digested by adding 1N sodium hydroxide (NaOH) and placed in an oven set at 40°C until dissolved. The radioactivity in each sample was determined by LSC.

Feces samples collected from male dogs at 0-24 (BDC dogs dosed IV) and at 24-48, 48-72, 72 96, 96-120, and 120-144 (intact dogs dosed IV) hours post-dose were pooled by group to generate 24- to 48-, 48- to 72-, 72- to 144-hour pooled samples for intact dogs dosed IV and 0- to 24-, 24- to 48-, and 48- to 120-hour pooled samples for BDC dogs dosed IV, including 0.2 to 2 % (equivalent percent by interval) of each sample by weight. A subsample (0.3 g) of each pool was digested by adding 1N NaOH and placed in an oven set at 40°C until dissolved.
Pooled bile and feces samples were analyzed by LC-^{14}C-HRMS with eluent fractions collected at 10-second intervals into 96-well plates containing solid scintillant. Radioactivity in each well was determined using TopCount analysis, and radiochemical profiles were generated based on radioactivity counts.

In Vivo Metabolite Profiling and Identification. Metabolite profiling and identification in plasma, urine, bile, and feces samples from rats and dogs were conducted by LC-^{14}C-HRMS. The LC and HRMS conditions used for analysis of rat samples are summarized in Supp. Table S3 and Supp. Table S4, and for dog samples in Supp. Table S4. For rat samples, the eluent following chromatographic separation was split with 75% of the flow directed to the fraction collector and remaining 25% to mass spectrometer and for dog samples, the eluent following chromatographic separation was split with 80% of the flow directed to the fraction collector and the remaining 20% to mass spectrometer. A total of 384 fractions were collected from rats and dogs at 10-second intervals into 96-well solid-scintillant-containing LumaPlates (Perkin Elmer). The LumaPlates were dried in a fume hood, and radioactivity in each well was determined using a TopCount reader (Perkin Elmer). The radiometric data was imported into and analyzed using Laura software (Perkin Elmer).

Table S3. LC-HRMS conditions (Method 1 used for rat profiling)

Ionization interface:	Positive ion heated electrospray interface (HESI)		
Controller:	Shimadzu/Prominence CBM-20A		
Pumps:	Shimadzu/Nexera LC-30AD		
Autoinjector:	Shimadzu/Nexera SIL-30ACMP (15°C)		
Column oven:	Shimadzu/Prominence CTO-20AC (50°C)		
Degasser:	Shimadzu/Prominence DGU-20A5R		
Mass spectrometer:	Thermo Fisher Scientific Q Exactive		
Fraction collector:	Leap Technologies PAL HTC-xt (15°C)		
HPLC column:	Phenomenex Kinetex C18, 4.6 x 250 mm, 5 µm		
Guard column:	Phenomenex C18, 3 x 4 mm		
Mobile phase A:	0.1% formic acid in water		
Mobile phase B:	methanol		
Gradient:	Time (minutes)	%A	%B
	0.0	90	10
	10.0	90	10
	55.0	25	75
	57.0	2	98
	60.0	2	98
	60.5	90	10
	68.0	90	10
Flow rate:	1.00 mL/minute; split ratio 25:75 mass spectrometer:fraction collector		
Survey scan:	*m/z* 300 - 1400 at 70,000 resolution		
Dependent scans:	MS^2 at 17,500 resolution		
Source voltage:	+ 4.0 kV		
S-Lens RF level:	65		

Table S4. LC-HRMS conditions (Methods 2 and 3 used for rat and dog profiling)

Binary Pump:	Agilent/1200 Bin Pump SL		
Degasser:	Agilent/1200 Degasser		
Autoinjector:	Agilent/1200 HiP-ALS SL (15°C)		
Column oven:	Agilent/1200 TCC SL (50°C)		
Mass spectrometer:	Thermo Scientific/LTQ Orbitrap XL		
Fraction collector:	Leap Technologies PAL HTC-xt (15°C)		
Ionization interface:	Positive electrospray interface		
HPLC column:	Phenomenex Kinetex C18, 4.6 x 250 mm, 5 µm		
Guard column:	Phenomenex C18, 3 x 4 mm		
Mobile phase A:	0.1% formic acid in water		
Mobile phase B:	methanol		
Gradient:	Time (minutes)	%A	%B
Methods 2 &3	0.0	90	10
	10.0	90	50
	55.0	25	75
	57.0	2	98
	60.0	2	98
	60.5	90	10
	68.0	90	10
Gradient:	Time (minutes)	%A	%B
Methods 2 &3	0.0	90	10
	10.0	50	50
	55.0	25	75
	57.0	2	98
	60.0	2	98
	60.5	90	10
	70.0	90	10
Flow rate:	1.00 mL/minute; split ratio 25:75 mass spectrometer : fraction collector		
MS Survey scan:	*m/z* 300 – 1500, at 30,000 resolution		
Data dependent scans:	Dependent scan 1: HCD MS^2 at 7,500 resolution (Method 2), CID MS^2 at 7500 resolution (Method 5) Dependent scan 2: CID MS^2 at 7,500 resolution (Method 2), CID MS^3 at 7500 resolution (Method 5) Dependent scan 3: CID MS^3 at 7,500 resolution (Method 2), CID MS^4 at 7500 resolution (Method 5) Dependent scan 4: CID MS^3 at 7,500 resolution (Method 3)		
Source voltage:	+5.0 kV		
Capillary voltage:	46 V		

CID, Collision induced dissociation; HCD, High collision energy dissociation.

Table S5. Summary of representative liquid chromatography-high resolution mass spectrometry data for LEN and its biotransformation products

Analyte	Proposed Identity	Representative RT (min)	Calculated *m/z*	Observed *m/z*	Difference (ppm)	Product ion (*m/z*)
LEN	LEN.1 & .2[a]	43.36, 44.82	968.1508	968.1519	1.1	889, 869, 790, 750, 662, 608, 529, 481, 402, 217
M1	LEN-desfluoro-cysteine-glycine conjugate	25.42	1142.1807	1142.1797	-0.9	1063, 1046, 1039, 960
M4, M8	Hydroxy-desfluoro-LEN-glutathione conjugate.1 & .2	27.8, 30.00	1271.2233	1271.2218	-1.2	1196, 1142, 1063, 1039, 960
M9, M10, M11	Dihydro-LEN-glutathione conjugate-1, 2 & 3	30.76, 31.34, 32.49	1275.2346	1275.2329	-1.3	1146, 1066, 923, 890
M13A & B[a]	LEN-glucuronide	34.50, 35.17	1144.1829	1144.1828	-0.1	889, 869, 790, 750, 662, 608, 529, 481, 402
M15	Hydroxy-LEN-1	35.17	984.1457	984.1444	-1.3	964, 885
M19	Hydroxy-LEN-2	39.33	984.1457	984.1465	0.8	964, 885, 865, 740, 467, 400
M20	N-[des-trifluoroethyl]-LEN	39.67	886.1478	886.1476	-0.2	708, 688, 447, 320
M29, M43[a]	LEN-pentose conjugate	36.19, 36.65	1100.1931	1100.1938	0.6	889, 869, 790, 750, 662, 608, 529, 481, 402
M26, M27[a]	LEN-hexose-conjugate	33.89, 34.64	1130.2036	1130.2046	0.9	889, 869, 790, 750, 662, 608, 529, 481, 402
P2[b]	Compound 699	53.5	906.1662	906.1682	-2.2	662, 528, 480, 401
P3[b]	Compound 699 + 14 Da	57.7	920.1472	920.1474	-0.2	559, 539, 433
P4[b]	Compound 668	59.2	890.1718	890.1732	-1.6	664, 609, 530, 482, 403, 217
	Compound 750		892.1619	892.1641	-2.5	662, 607, 528, 480, 401

[a]Atropisomer pair
[b]Structures of P2, P3, P4 are shown in Supp. Fig. 2.

Figure S2. **Summary of late-eluting LEN-derived product peaks formed due to radiolysis/photolysis**

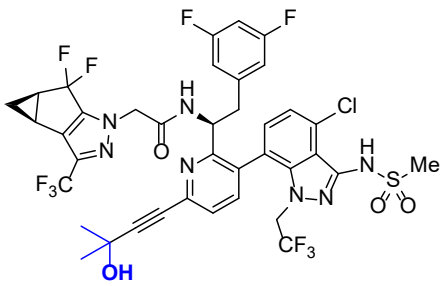
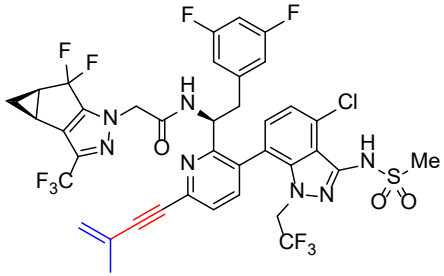
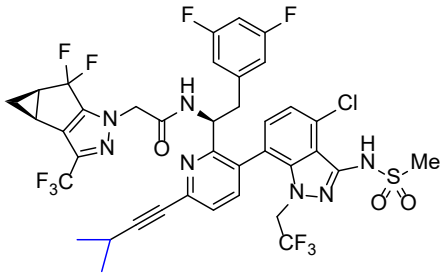
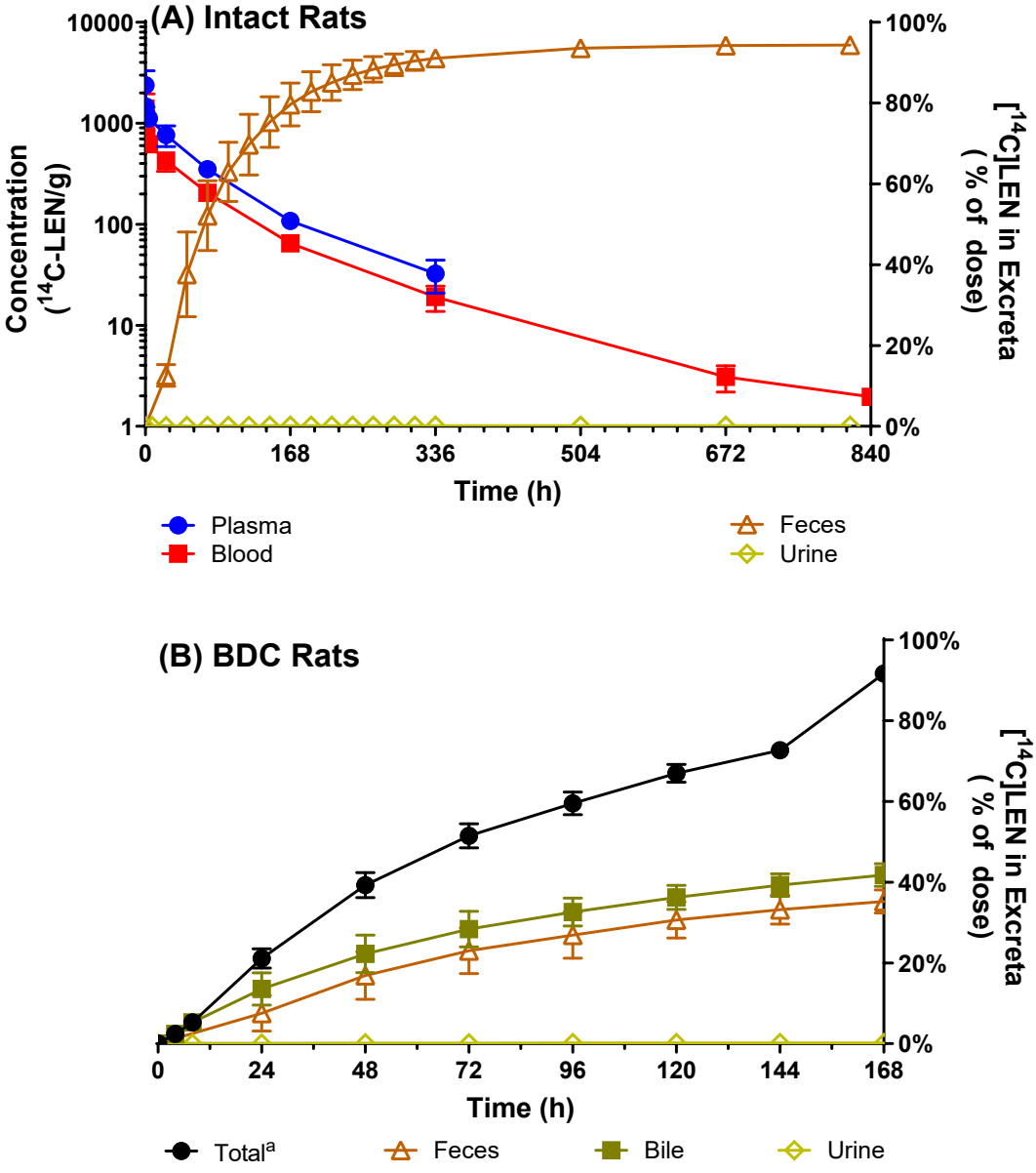
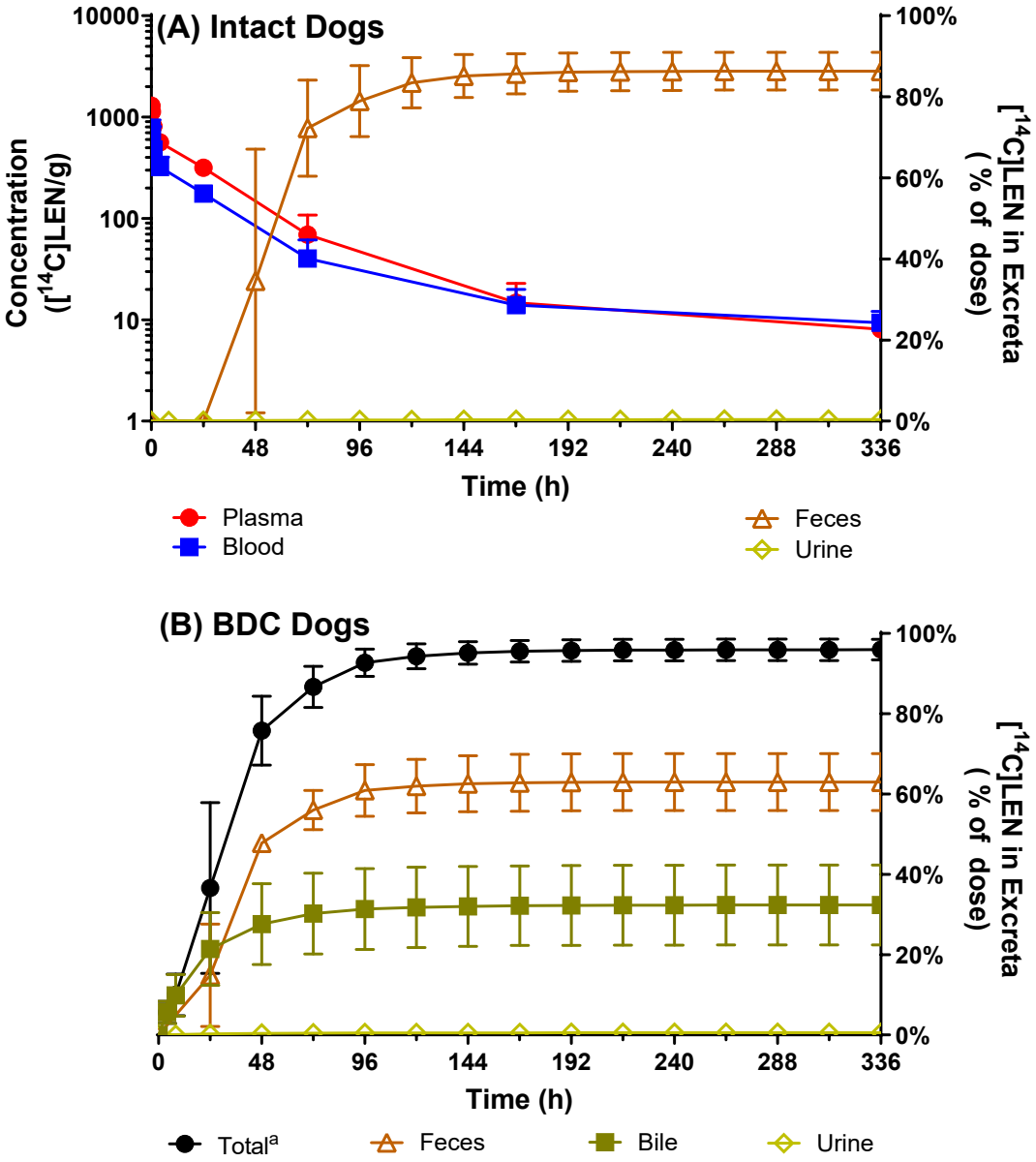
P2 Compound 699	P3 M31 +14 Da	P4 Compound 750	P4 Compound 668
			

Figure S3. Concentration-time profile of total radioactivity in blood and plasma following a single IV administration of [^{14}C]LEN at 3 mg/kg in intact (A) and BDC (B) WH rats (plasma/blood, *n* = 2 per time point, mean; feces/urine, n=3, mean ± SD).



SD, standard deviation; WH, Wistar Han
For the last time point at 168 hours in BDC rats, total excreta include [^{14}C]LEN recovered from the cage rinse, cage wash, cage wipe, and carcass.

Figure S4. Concentration-time profiles of total radioactivity in blood, plasma, and excreta following a single IV administration of [^{14}C]LEN at 1 mg/kg in intact (A) and BDC (B) beagle dogs (mean ± SD, n = 3)



SD, standard deviation
In intact dogs, blood and plasma were analyzed at specified times through 672 hours postdose. Concentrations in blood and plasma were below the limit of quantitation after 336 hours postdose.
For the last time point at 336 hours in BDC dogs, total excreta include [^{14}C]LEN recovered from the bile canula, cage debris, cage rinse, and cage wipe.