GILEAD
Creating Possible

The Story of Lenacapavir (LEN), a First in Class Capsid Inhibitor, From Discovery to Clinical Development

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Aspirations for Long-Acting Injectables in HIV Therapy

Today's Antiretroviral Medicines Are Highly Effective But Dosing Optionality is an Important Unmet Need

Treatment

> *"I don't like being reminded every single day that I'm HIV positive"*
>
> *- Person Living With HIV (PLWH)*[1]

~60% of People Living with HIV selected less frequent dosing as greatest unmet need[1]

Prevention

> *"You really have to take the pills every day, and I just could not do that."*
>
> *- Discontinued PrEP User*[2]

50%↑ in PrEP utilization reported if longer-acting oral and injectable options become available[2,3]

20+ pills a day → **Single tablet regimens** → **Long-acting injectables**

Pill burden

STR's established in 2006

Adherence issues

1. HIV Patient Long-Acting Opportunity patient quant survey, 1Q 2016, N=100 (US, FR, UK)
2. HIV Prevention Global HCP Demand Estimation 2020
3. HIV Prevention Consumer Market Research 2019-2020; PrEP = Pre-Exposure Prophylaxis.

LAI Product Profile

Optimal long acting ARVs

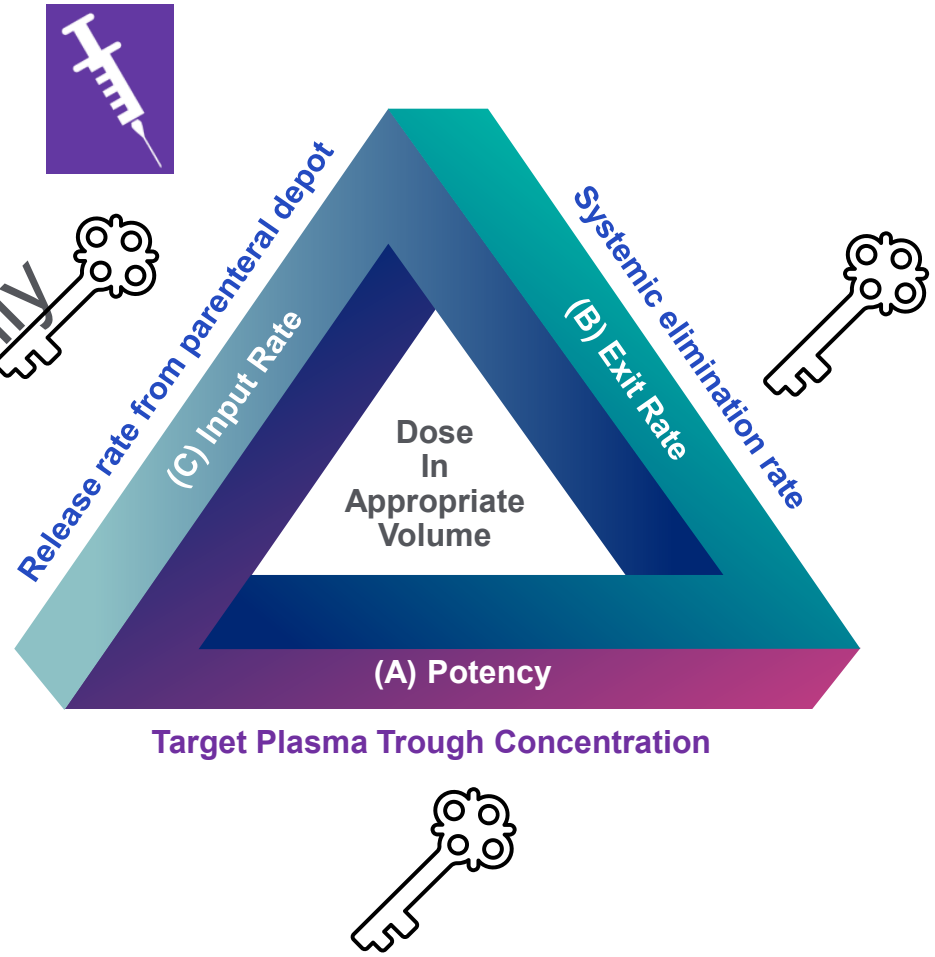
- *Long dosing interval (monthly or less frequent)*
- *Low volume subcutaneous injection*
- *Capacity for self-administration*
- *Low pain, no injection site reaction*

Ideal properties of long acting ARVs

- *Highly potent*
- *Sustained exposure for the target duration*

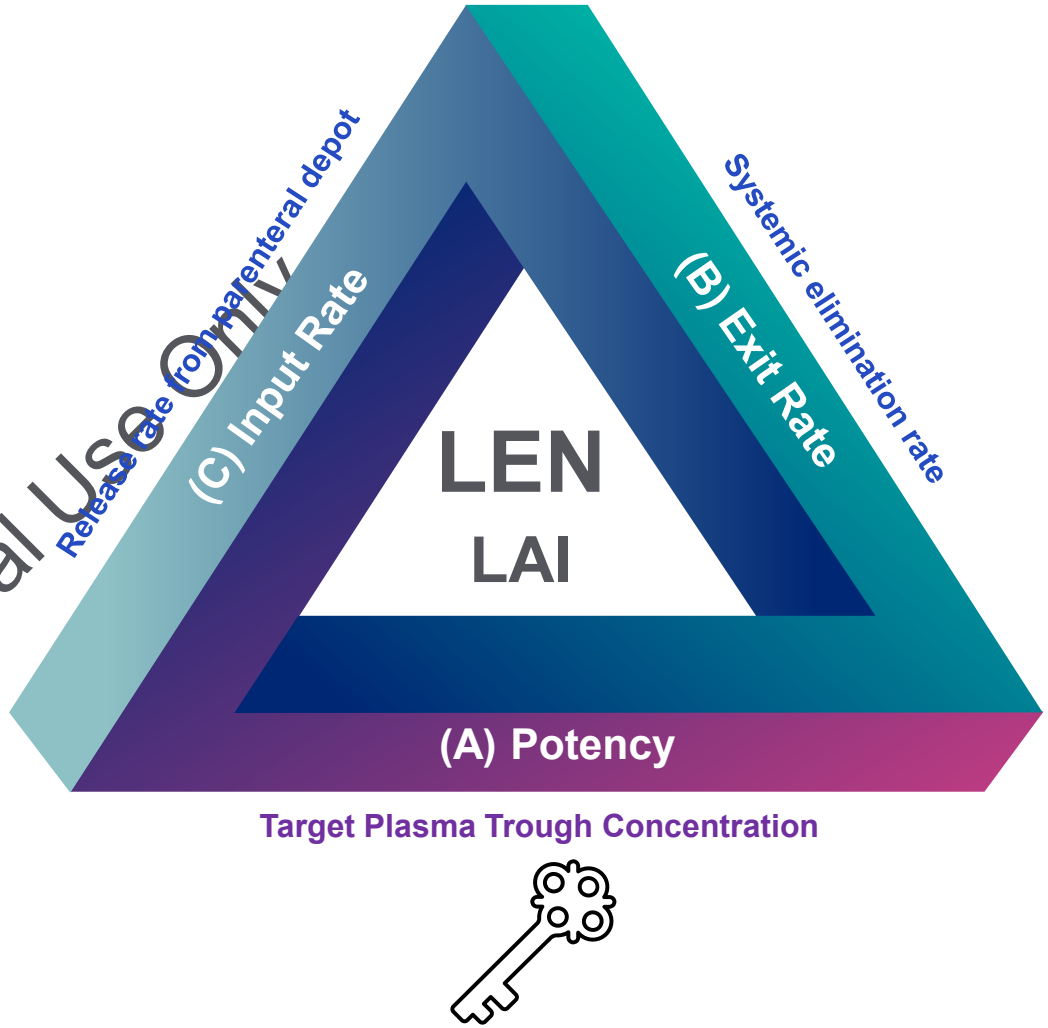
ARV = antiretroviral; LAI = long acting injectable

Three Keys to Enable a LAI

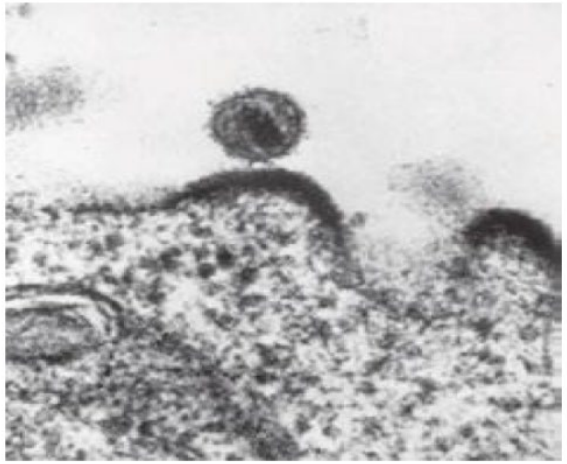


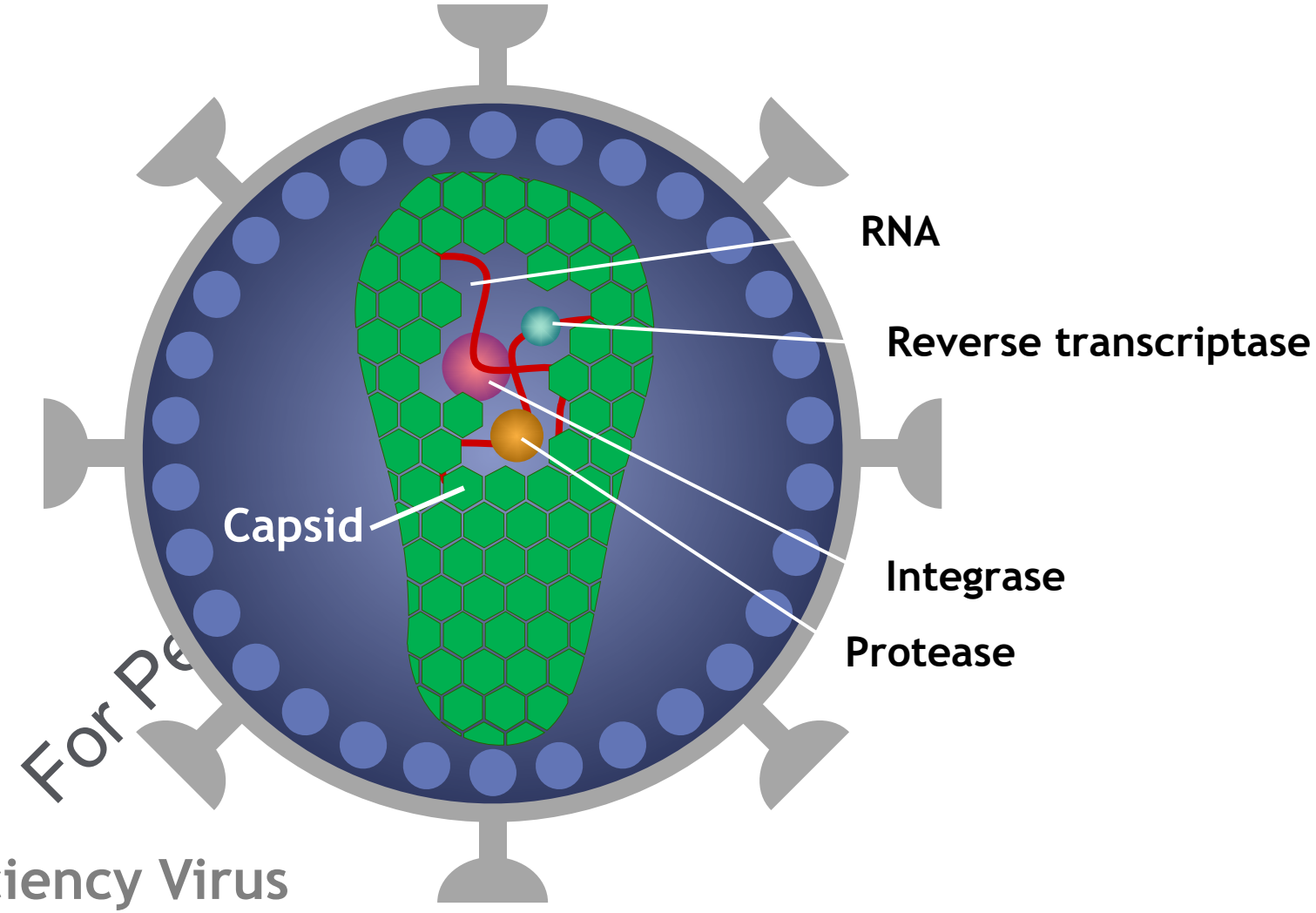
LAI display “flip-flop” PK – Input Rate << Exit Rate

LAI Key 1: Target Potency



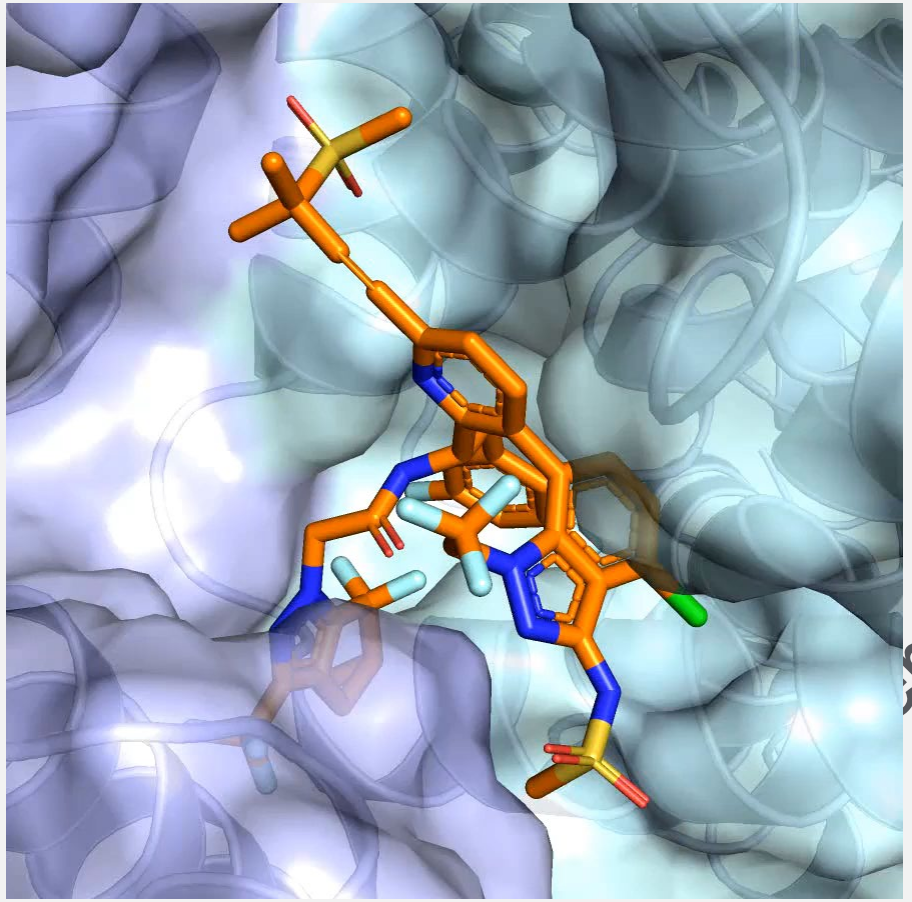
Target - What is Capsid?

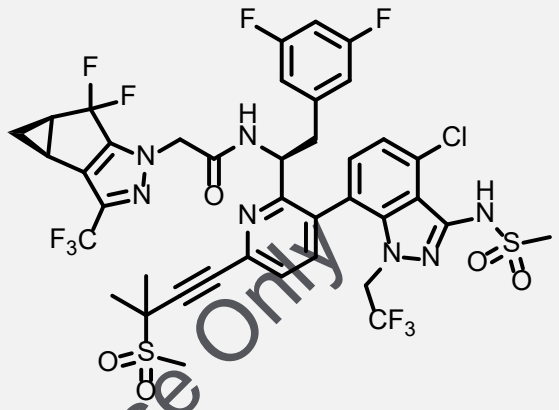




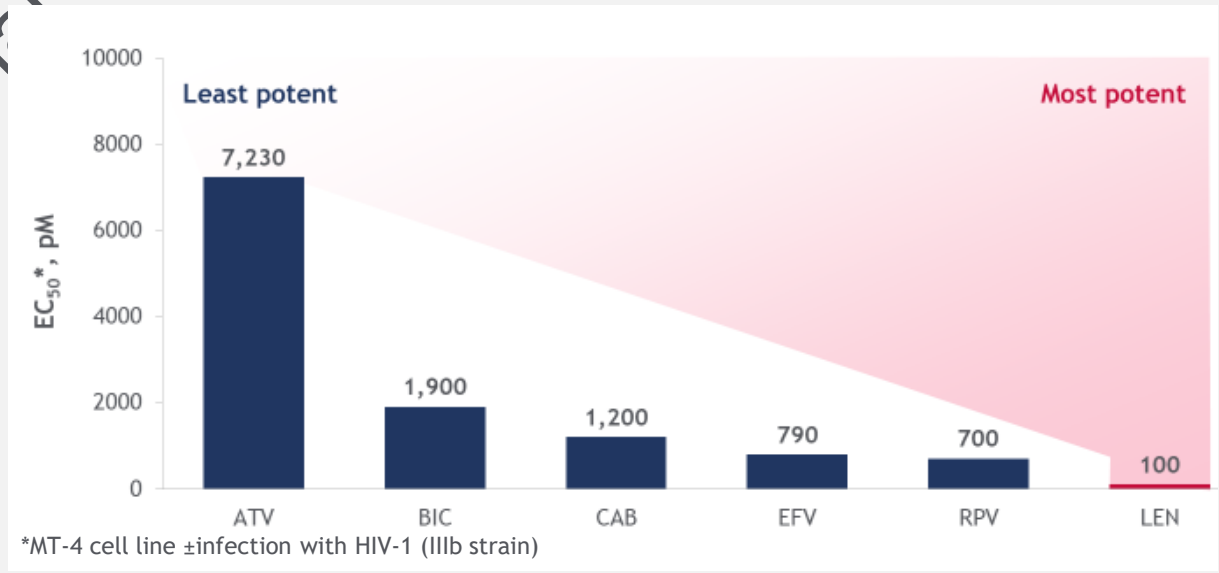
Human Immunodeficiency Virus (HIV)

LEN Discovery: 10+ years & 3000+ Compounds led to LEN





- MW 968 g/mol
- cLogP 6.0
- 12 hydrogen bond acceptors
- Polar surface area 175 Å^2
- 5 aromatic rings; 7 rings
- 2 hydrogen bond donors
- 15 rotatable bonds
- 10 fluorine atoms



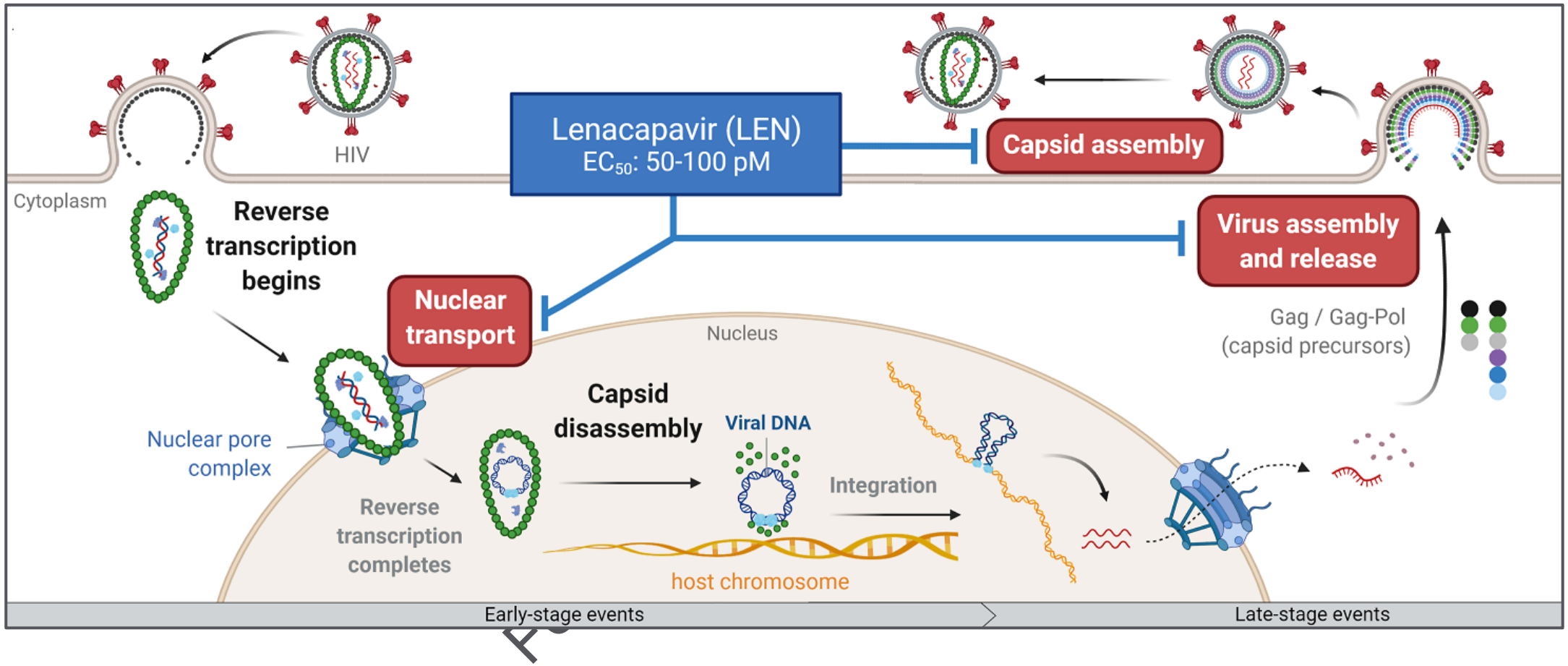
High shape complementarity contacting more than 2,000 Å^2 of buried protein surface area

LEN binding alters assembly/disassembly of core

Adapted from Eda Canales, PDN#002351

ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; EFV = efavirenz; RPV = rilpivirine

LEN Targets Multiple Stages of HIV Replication Cycle to Achieve Picomolar Potency

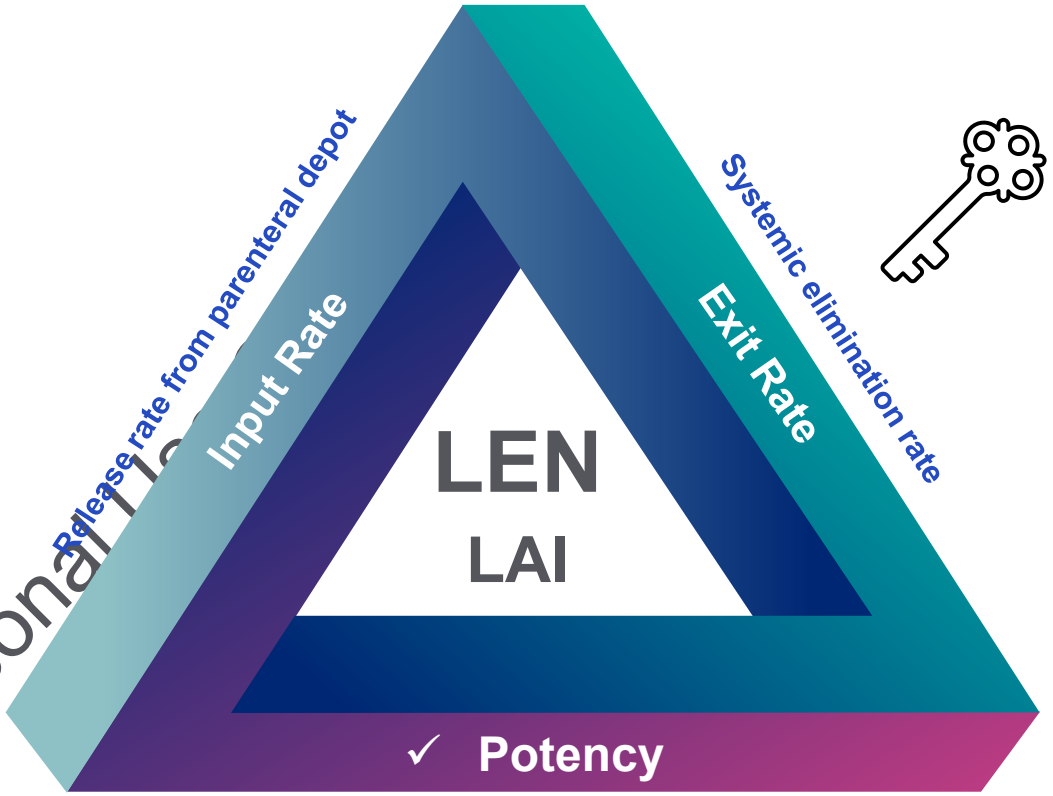


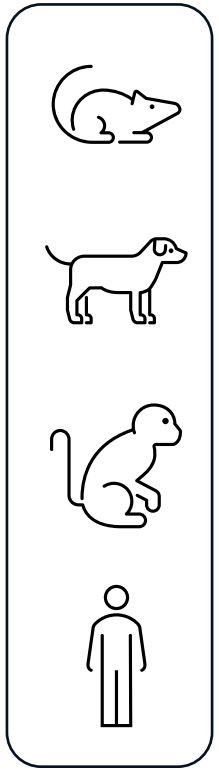
- ☑ Orthogonal mechanism of action – active against all major HIV-1 subtypes
- ☑ Picomolar cellular potency; translates to a human serum $paEC_{95}$ = 4.0 nM

EC_{50}, half-maximal effective concentration; $paEC_{95}$, protein-adjusted 95% effective concentration

Link et al. *Nature* 2020; Bester et al. *Science* 2020

LAI Key 2: Exit Rate

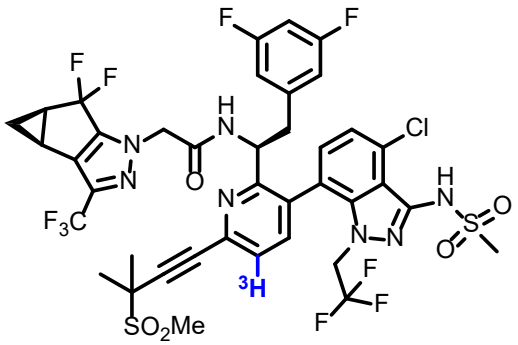




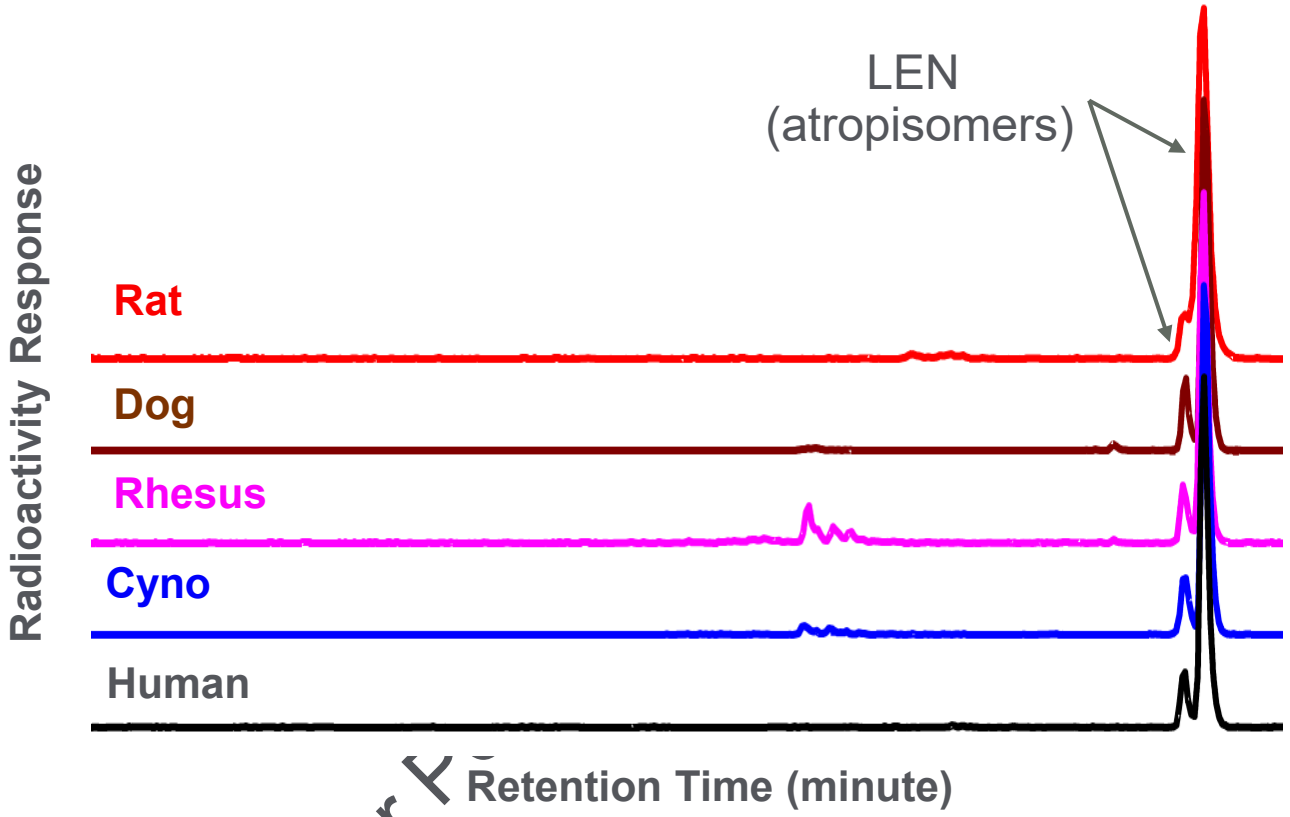
Weber et al. *Clin Pharmacokin*, Feb 2024; Zheng et al, JPET, Oct 2024

LEN Demonstrates High Metabolic Stability in Hepatocytes

[^{3}H]LEN



- ^{3}H HLM Cl = 0.01 L/h/kg
- LEN too stable to determine CL with LC-MS in vitro assay



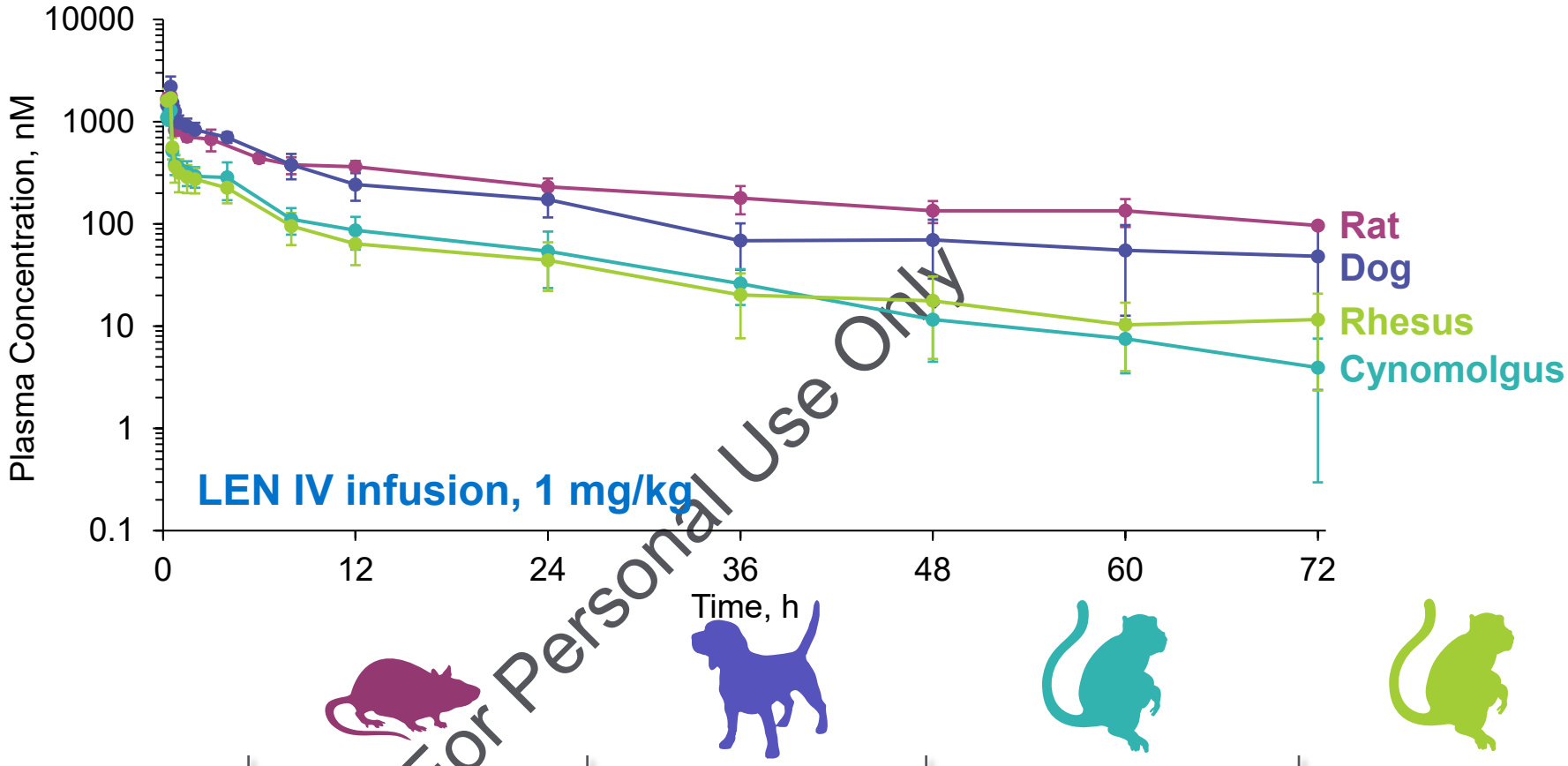
Predicted Hepatic Extraction (% of liver blood flow)

Rat	< 1%
Dog	3%
Rhesus	3%
Cyno	6%
Human	< 1%

- In nonclinical species, limited turnover was observed
- Lowest turnover was observed in human
- LEN predicted to have low hepatic metabolic CL in human

Zheng et al, JPET, Oct 2024

LEN Nonclinical PK - Low Systemic CL & Moderate V_{SS}



Mean (n =3)	Rat	Dog	Cynomolgus NHP	Rhesus NHP
CL, L/h/kg	0.055	0.073	0.24	0.26
V_{SS} (L/kg)	1.8	1.6	2.7	5.2
$T_{1/2}$ (h)	28	22	12	29

Zheng et al, JPET, Oct 2024

LEN In Vivo Observed CL Values Were Higher Than In Vitro Predicted CL Values

Species	Mean CL, L/h/kg		
	Predicted $CL_{in\ vitro}$*		Observed $CL_{in\ vivo}$*
	microsomes	hepatocytes	
Rat	0.01	0.02	0.055
Dog	0.02	0.06	0.073
Cynomolgus	0.04	0.05	0.24
Rhesus	0.13	0.15	0.26

* Predicted in vitro CL using ^{3}H-labeled LEN; Observed in vivo CL following IV infusion of LEN (n = 6 to 9)

(A) How to predict human PK? (B) Mechanistic understanding of IVIV disconnect

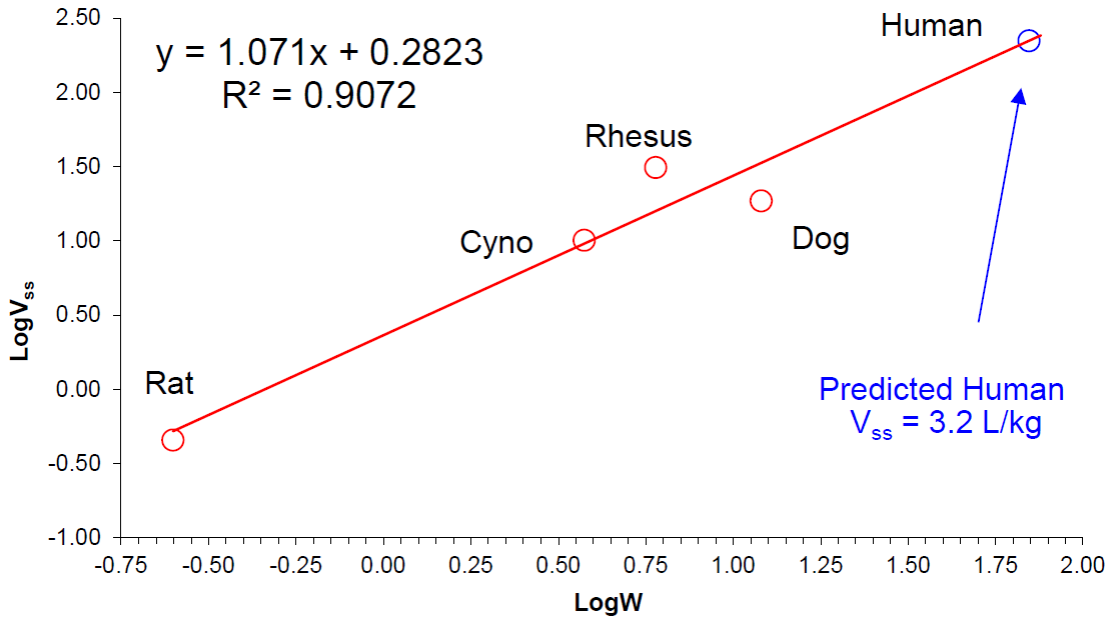
Zheng et al, JPET, Oct 2024

LEN Human Predicted PK

CL = in vitro/in vivo (IVIV) "disconnect" + hPredCL

	CL (L/h/kg)		$\Delta CL = Cl_{in\ vivo} - Cl_{in\ vitro}$	
	^3H in vitro	in vivo	L/h/kg	% LBF†
rat	0.02	0.055	0.035	1
dog	0.06	0.073	0.013	1
cyno	0.05	0.24	0.19	11
rhesus	0.15	0.26	0.11	4
human	0.01	(0.01 + 0.05) Pred = 0.06	Avg ΔCL 0.05 L/h/Kg	Avg ΔCL 16/4 = 4%

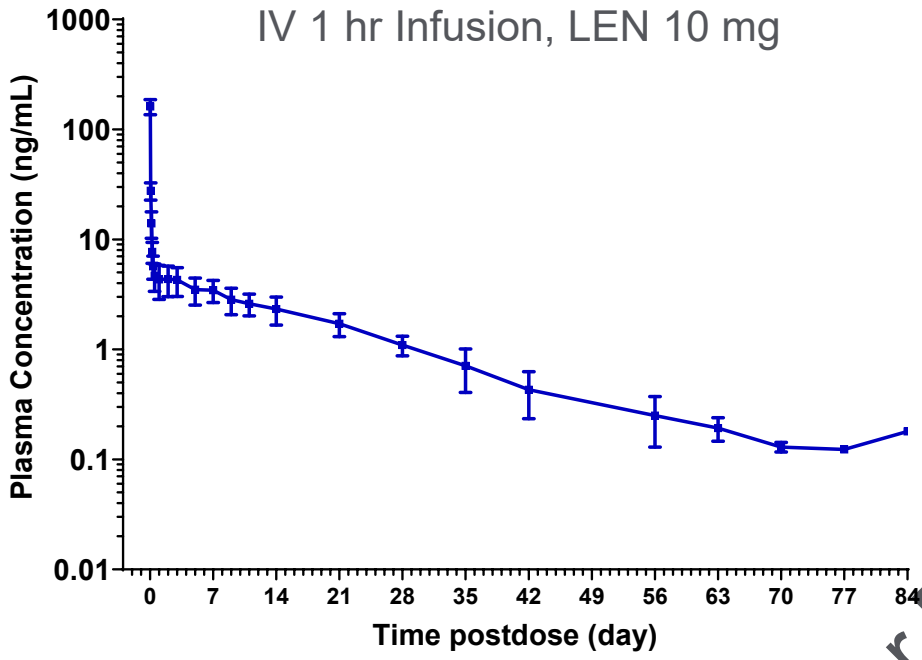
V_{ss} by Allometric Scaling



Predicted Human Parameters: **CL = 0.06 L/h/kg; V_{ss} = 3.2 L/kg**; MRT = 54 h; $T_{1/2}$ = 37 h

† liver blood flow (L/h/kg)

LEN Human Observed IV PK



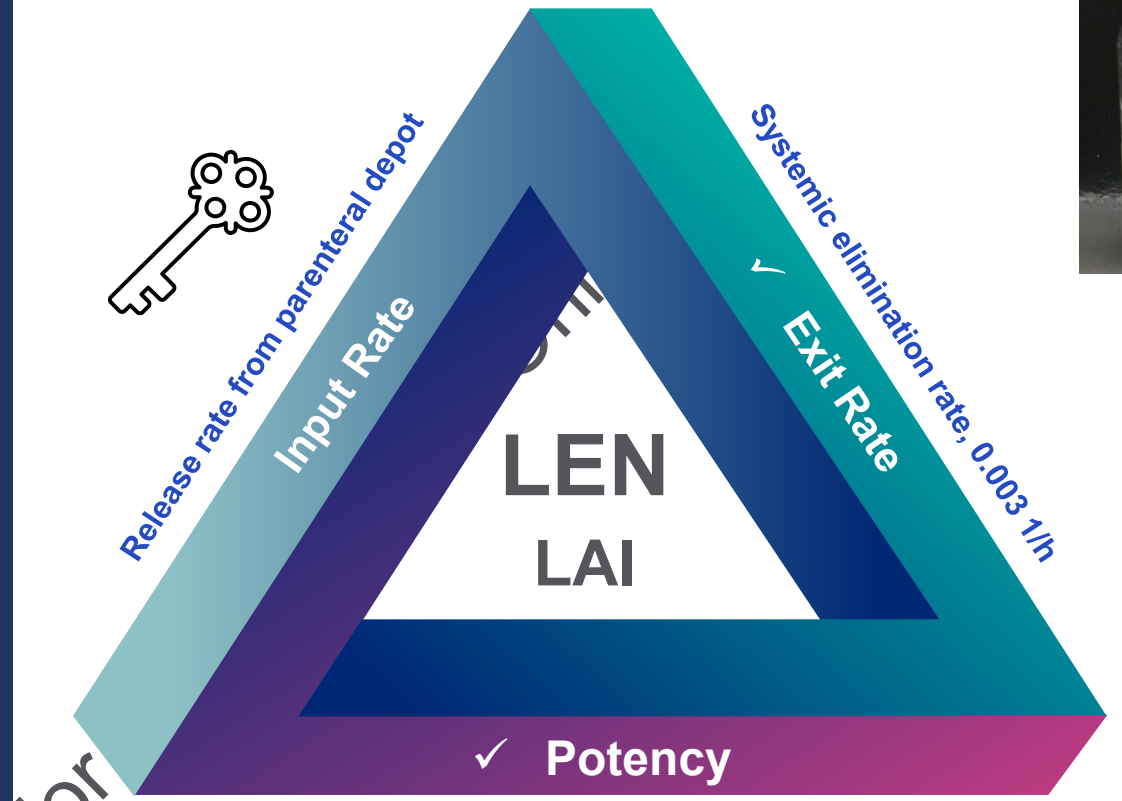
Plasma PK (n = 8)	Mean
$AUC_{0\text{-inf}}$	2340 h*ng/mL
λ_z	0.003 1/h
CL	0.06 L/h/kg)
Terminal $T_{1/2}$	274 h (11.4 d)
V_z	24.3 L/kg
V_{SS}	23.8 L/kg

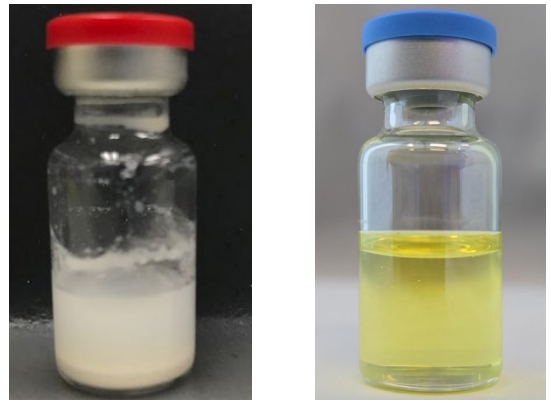
- Distinct bi-phasic PK

- Observed CL in-line with predicted CL
- Observed V_{SS} is 7.4-fold higher than predicted V_{SS}
- Terminal $T_{1/2}$ 11.4 days !!
- Systemic elimination rate 0.003 1/h

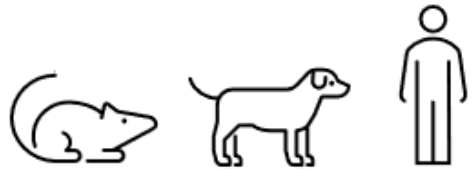
Weber et al. *Clin Pharmacokin*, Feb 2024

LAI Key 3: Input Rate Following SC Administration





Formulations
- Aqueous suspension
- PEG/water solution



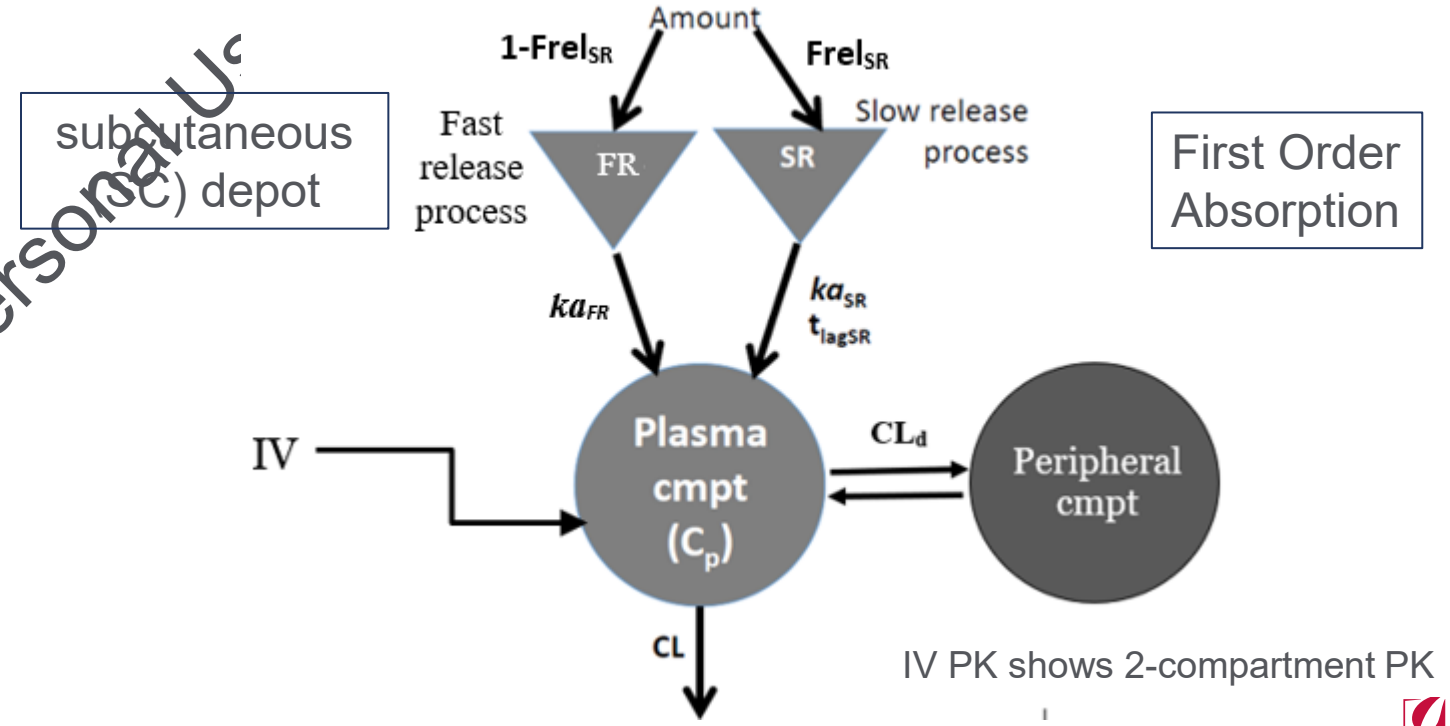
Long Acting Pharmacokinetics

SC = subcutaneous

Subramanian et al., *Mol Pharmaceutics*, Dec 2023

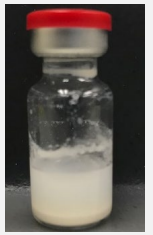
PK Modeling Informs Input Rate ($k_{release}$) and Exit Rate ($k_{elimination}$)

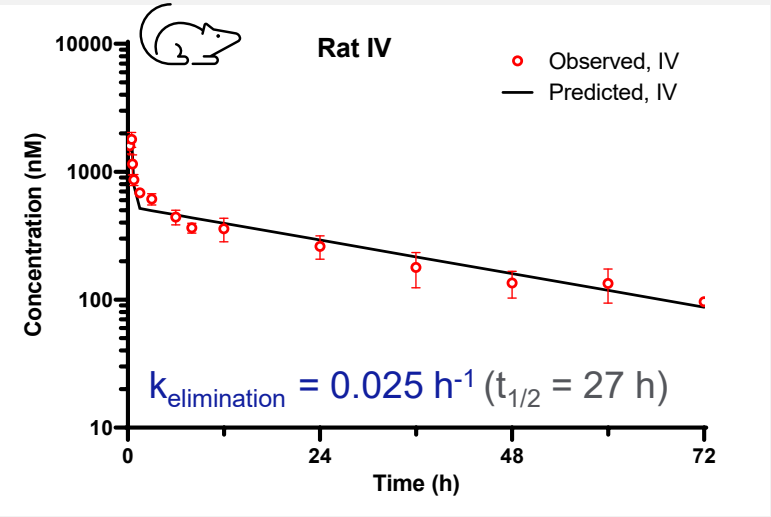
1. Noncompartmental Analysis (NCA)
   - SC PK - $k_{release}$ of the dissolution-limited “slow release” process from terminal phase
   - IV PK - $k_{elimination}$, systemic elimination rate
2. Two-compartment analysis (CA) Parallel Absorption Model with simultaneous fit of IV and SC PK
   - $k_{release}$ of the “slow release” process
   - k_{fast} of the initial “fast release” process
   - Fraction of dose released via each process
   - $k_{elimination}$, systemic elimination rate

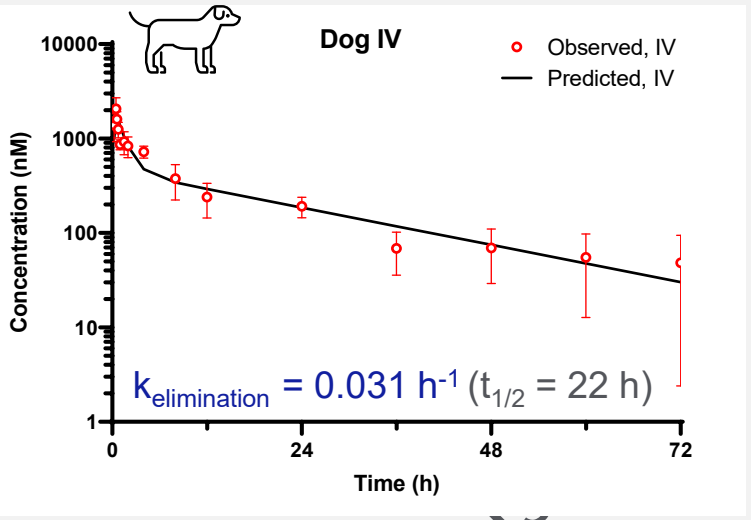


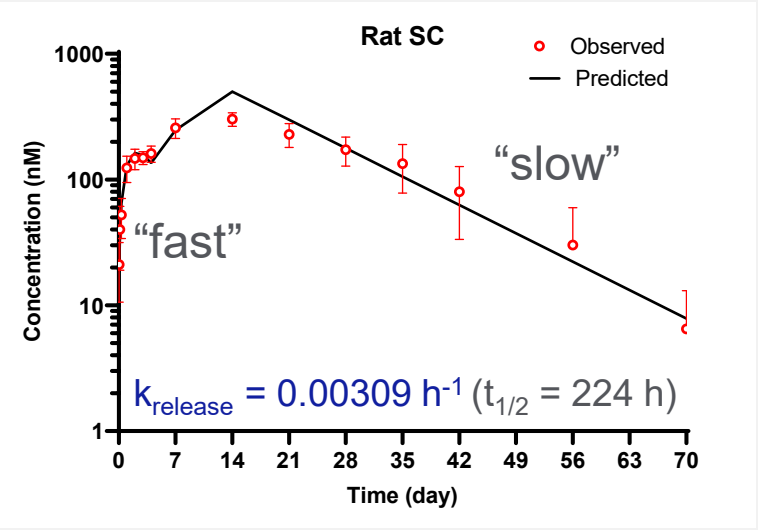
Subramanian et al., *Mol Pharmaceutics*, Dec 2023

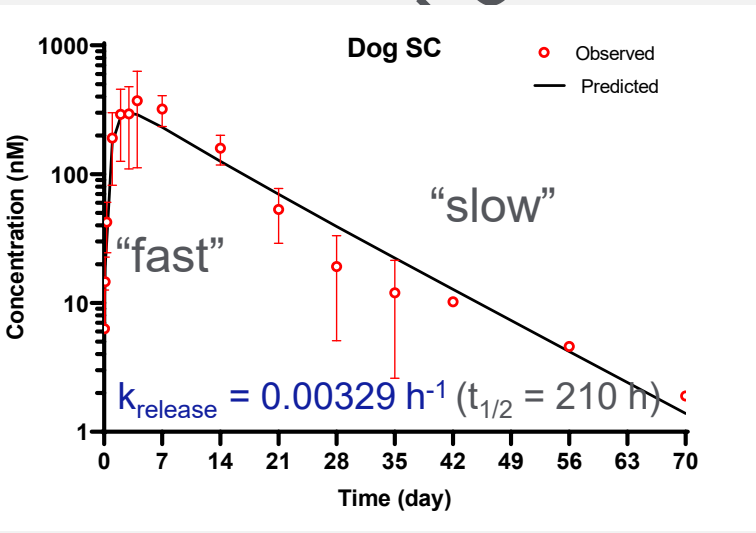
SC PK following 100 mg/mL Suspension Formulation







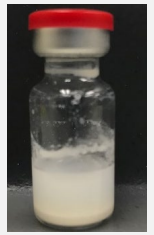


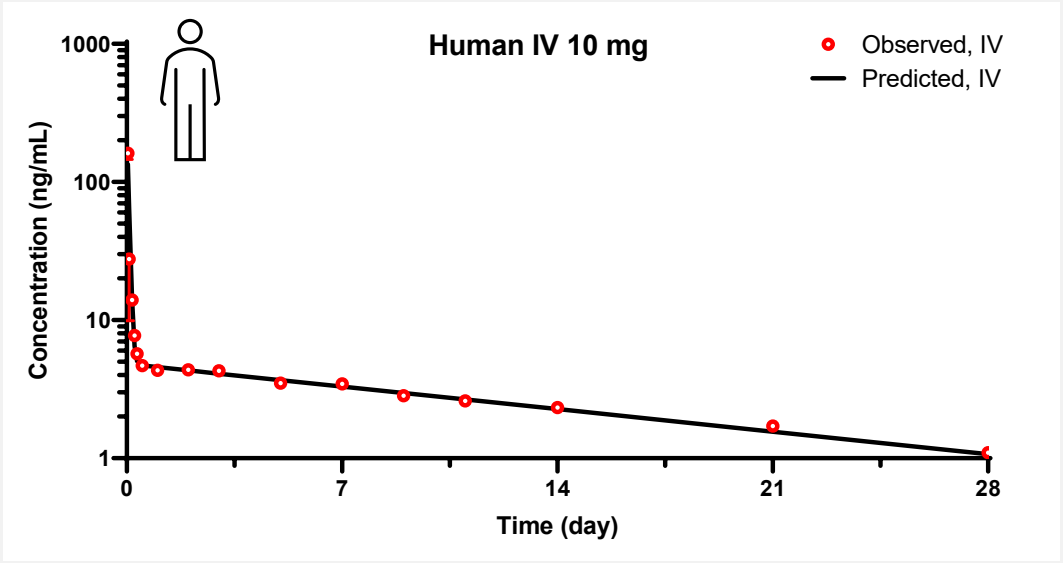


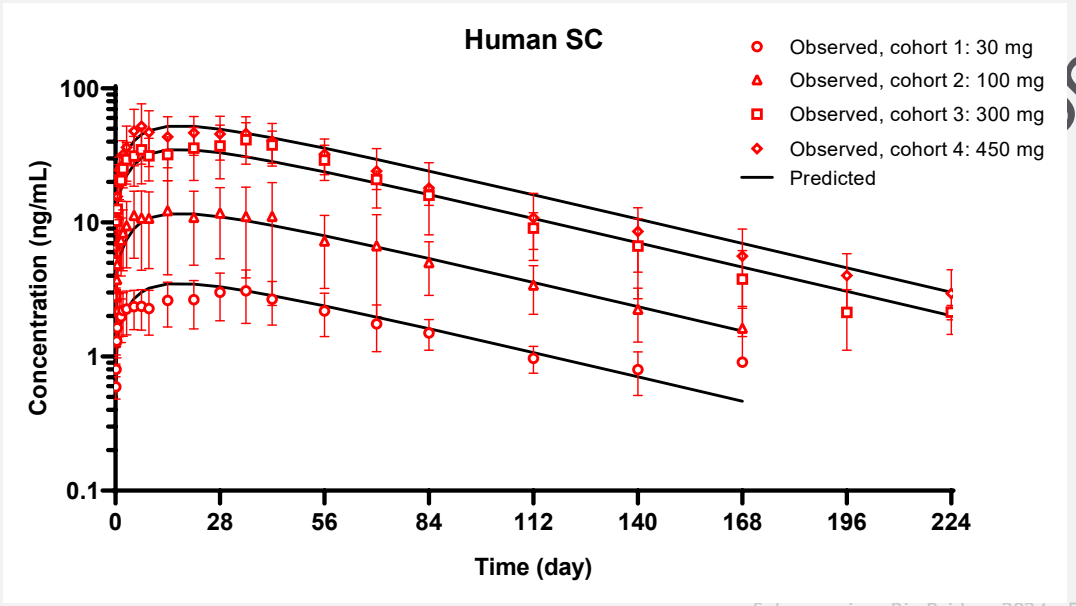
- No unintended rapid drug release; consistent with low aqueous solubility (< 1 µg/mL) & high LogD (3.7)
- Dissolution limited PK – flip-flop PK
- Well tolerated – systemic and injection site (local)
- Flip-flop PK - $k_{release}$ << $k_{elimination}$
- Dissolution limited PK provides sustained LEN release
- Fraction of dose released via the "slow" release – 88% - 91%

Subramanian et al., *Mol Pharmaceutics*, Dec 2023

Human PK following SC Administration of 100 mg/mL Suspension Formulation



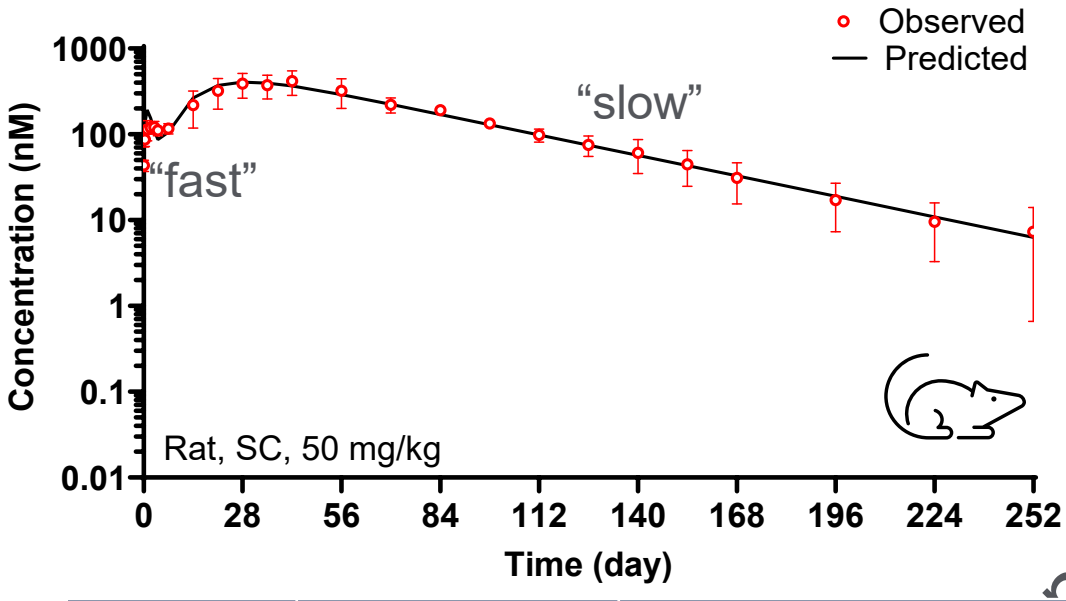


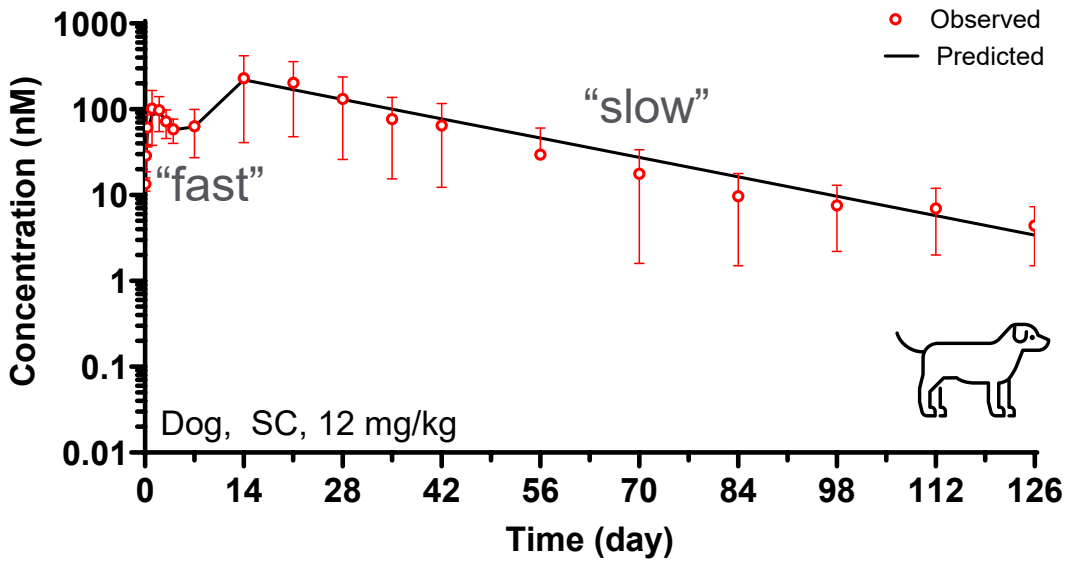


- Human $k_{release}$ similar across dose-range
- Flip-flop kinetics - $k_{release}$ << $k_{elimination}$
- Dissolution limited PK
- Well tolerated – systemic and injection site (local)
- Human $k_{release}$ < nonclinical $k_{release}$
  - Rat – 0.00309 h^{-1} ($t_{1/2}$ = 224 h; 9.3 d)
  - Dog – 0.00329 h^{-1} ($t_{1/2}$ = 210 h; 8.8 d)
  - Human – 0.000623 h^{-1} ($t_{1/2}$ = 1112 h; 46 d)

Subramanian et al., *Mol Pharmaceutics*, Dec 2023

Nonclinical PK - Subcutaneous LEN Single Dose PK with Optimized Solution Formulation (309 mg/mL)





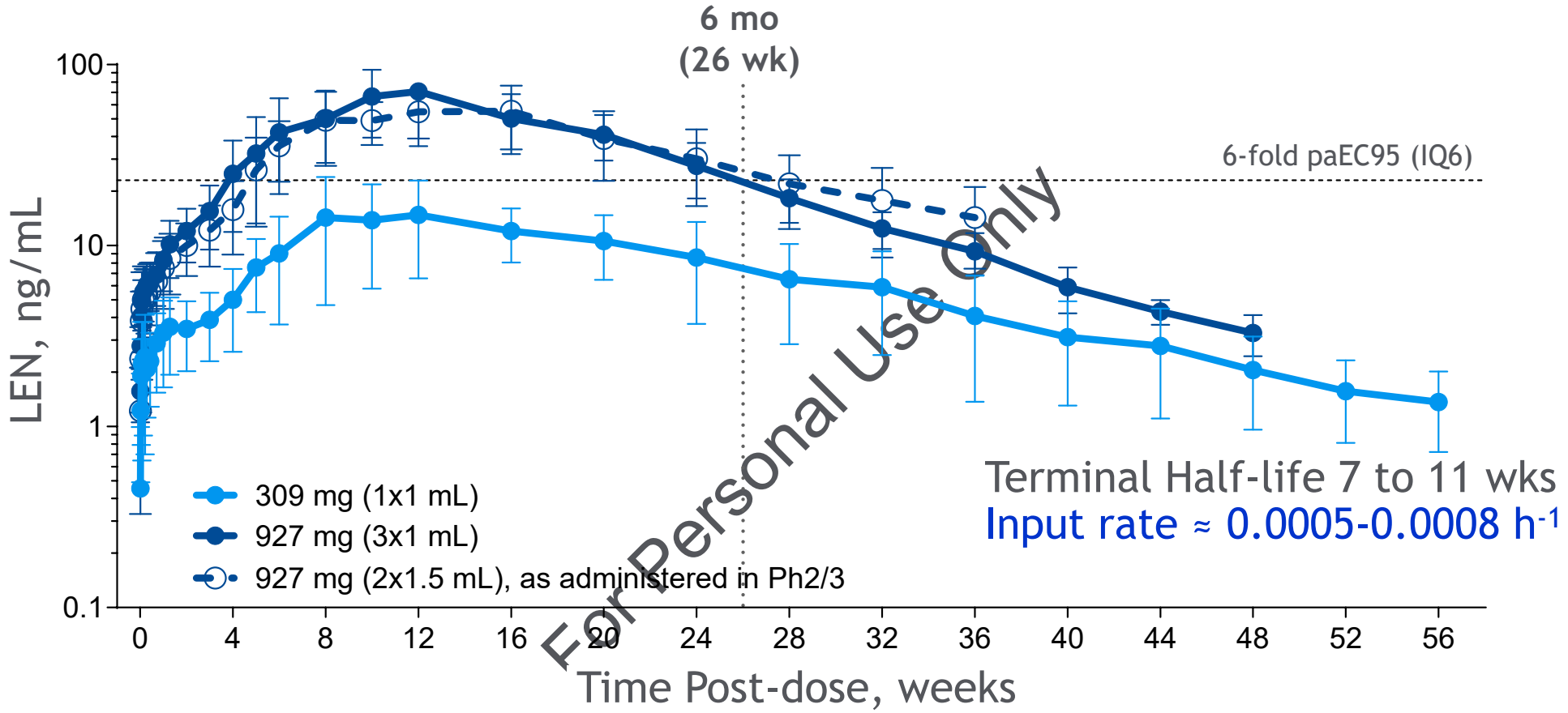
Species	Systemic Elimination	SC Depot Release Via Direct "Fast" Process			SC Depot Release Via Indirect "Slow" Process				
	$k_{elimination}$ (h^{-1})	k_{direct} (h^{-1})	$t_{1/2}$ (d)	$Frac_{direct}$	$k_{indirect}$ (h^{-1})	$t_{1/2}$ (d)	MTT (d)	$Frac_{indirect}$	F%
Rat	0.016	0.069	0.4	0.02	0.000818	35.3	15	0.98	75
Dog	0.023	0.014	2.1	0.06	0.0015	19.2	7.3	0.94	80

$k_{elimination}$ = 0.693/terminal $t_{1/2}$ from IV PK; $t_{1/2}$ = 0.693/k_{direct} or indirect; MTT, mean transit time = (no. of transit compartments + 1)/k_{tr}; F% = total fraction release

- Flip-flop kinetics: slow process input rate ($k_{indirect}$) << systemic exit rate ($k_{elimination}$)

Subramanian et al, *Mol. Pharm.*, Dec 2023

Human PK - LEN Single Dose Subcutaneous PK with Optimized Solution Formulation (309 mg/mL)

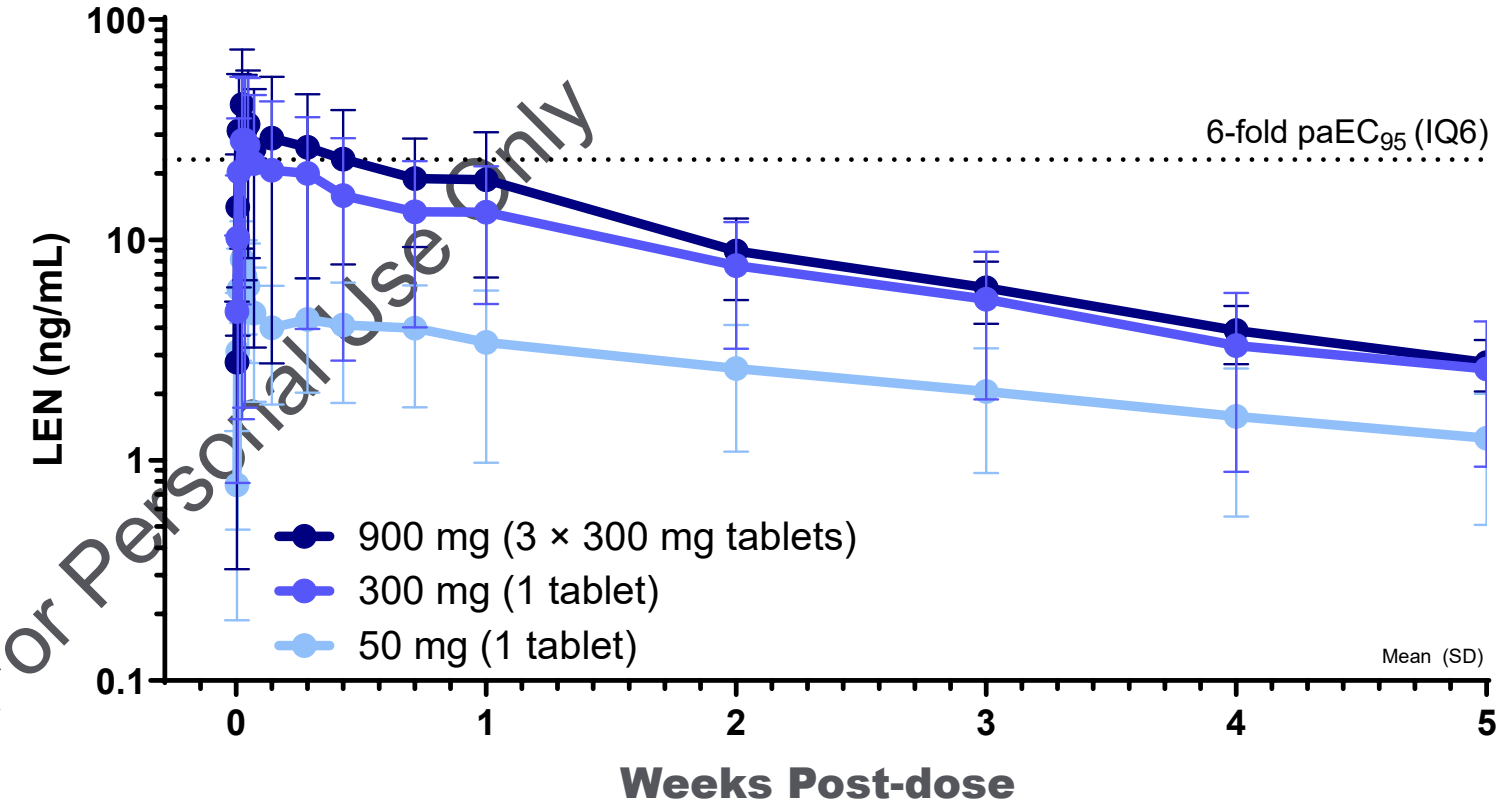


- ✓ Flip-flop kinetics: slow process input rate (~ 0.0005 h^{-1}) << systemic exit rate (0.003 h^{-1})
- ✓ Sustained exposure for the target (Q6M) duration

Dvory-Sobol H, et al. Curr Opin HIV/AIDS 2022

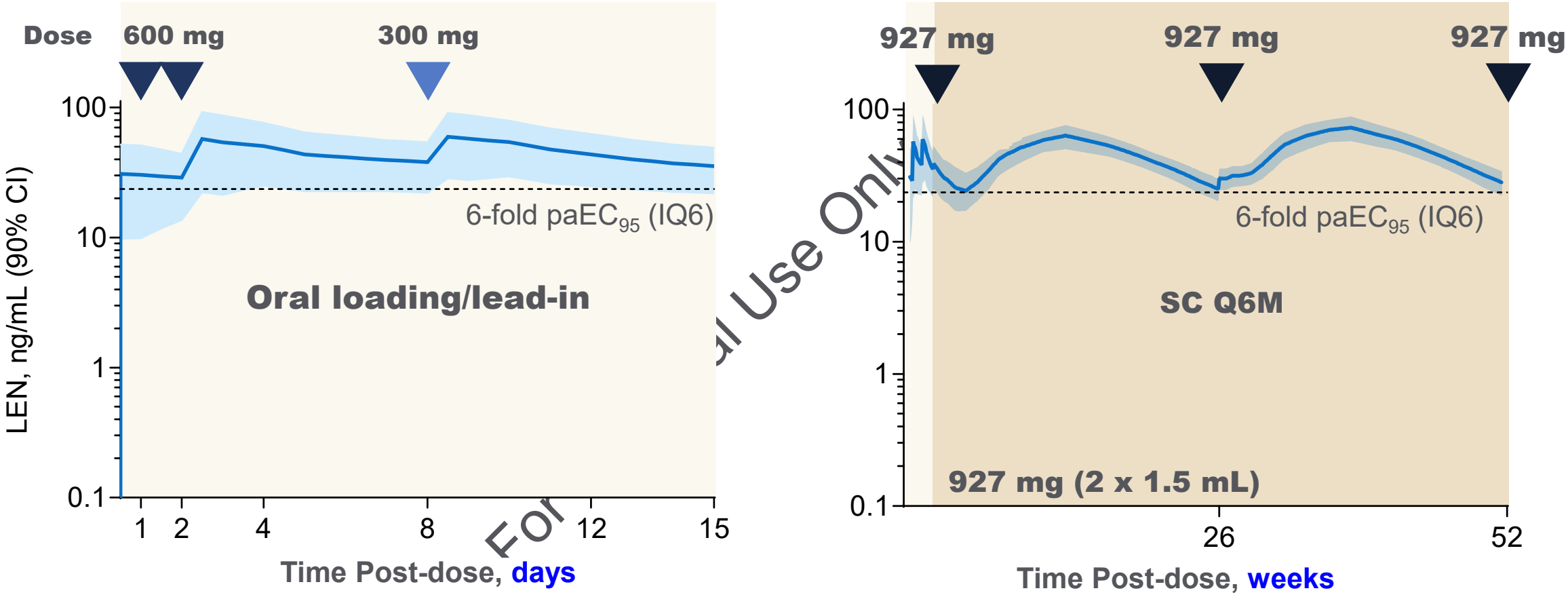
Lenacapavir PK Following Single Oral Dose

- Half-life ~ 12 days
- Oral tablet (300 mg) can be used for:
  - PK loading
  - Lead-in prior to SC injection



IQ, inhibitory quotient; $paEC_{95}$, protein binding-adjusted 95% effective concentration.
Dvory-Sobol H, et al. Curr Opin HIV/AIDS 2022

Putting Oral and Subcutaneous together
Predicted LEN PK for Approved LEN regimen



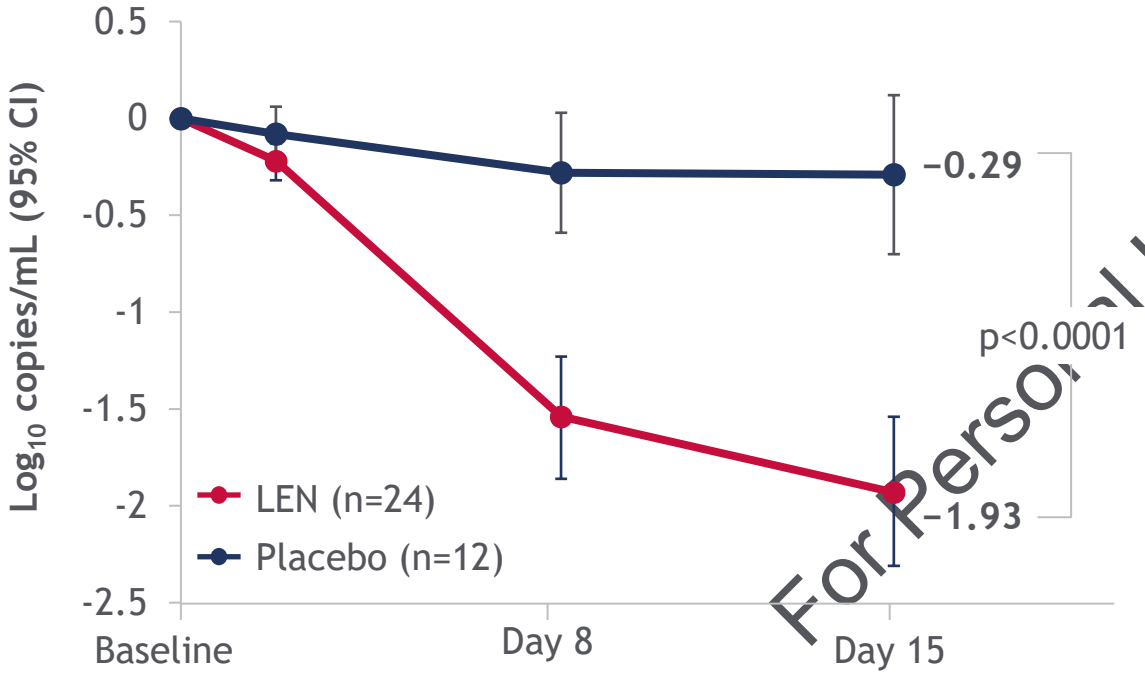
Approved alternate regimen: day 1 – 927 mg SC (2 x 1.5 mL), 600 mg oral; day 2 – 600 mg oral; 927 mg SC every 26-wks

CI, confidence interval. Dvory-Sobol H, et al. Curr Opin HIV/AIDS 2022

Ramesh Palaparthy; Dose Regimen Source: Sunlenca Drug Label (fda.gov)

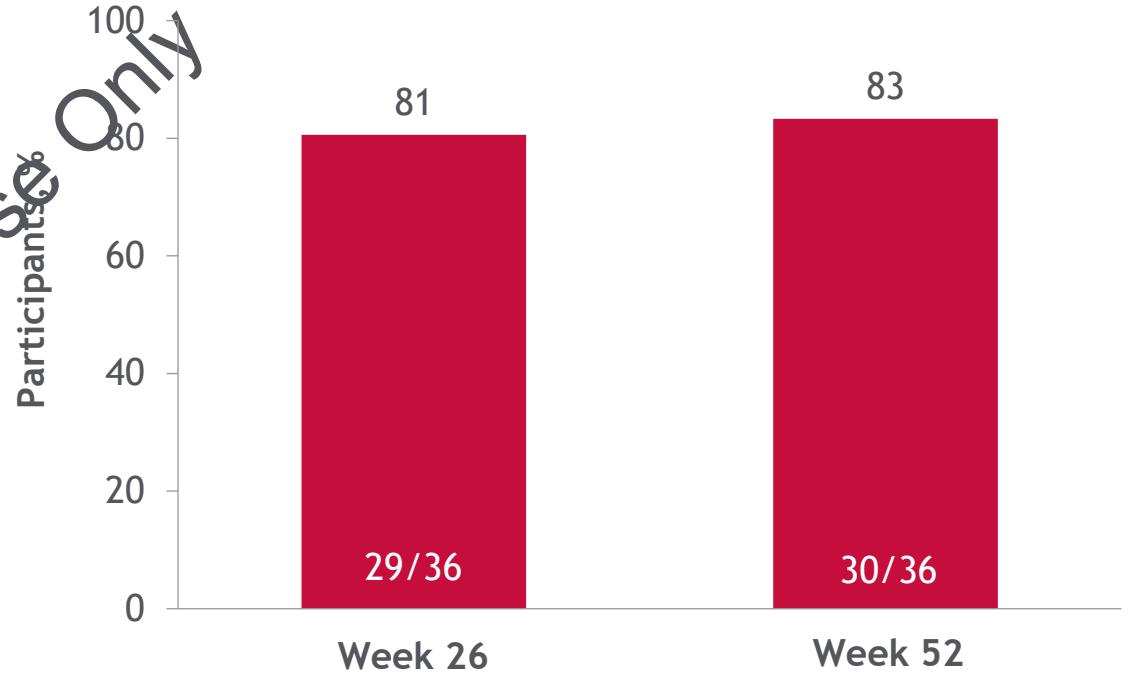
LEN for Treatment: Potent and Highly Efficacious In People with Multidrug Resistant HIV

During 14-day Functional Monotherapy Period (while continuing failing therapy)



Change in HIV-1 RNA

During 26 and 52 weeks of Maintenance Period (plus optimized background therapy)

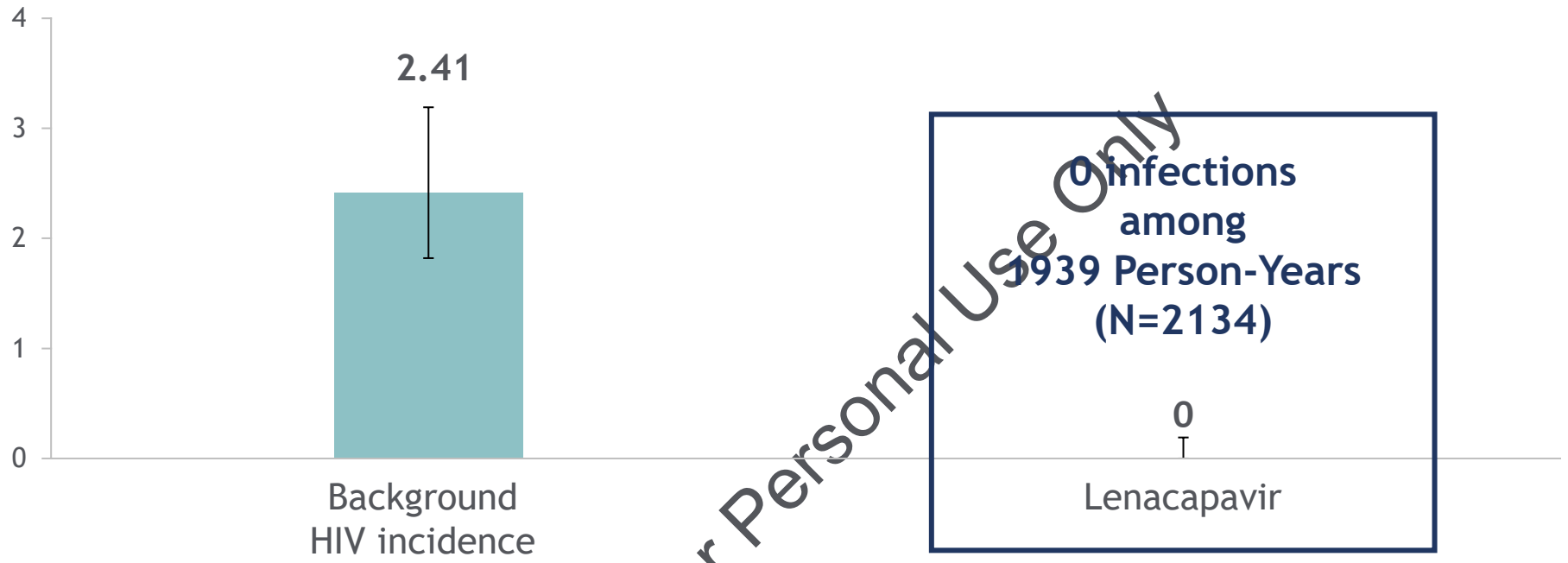


HIV-1 RNA <50 copies/mL

LEN for Prevention: Highly Efficacious

PURPOSE 1

HIV Incidence per 100 Person-Years (95% CI)[a,b]



Standing ovation at a scientific meeting last month

The NEW ENGLAND JOURNAL of MEDICINE

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

The New York Times

New Drug Provides Total Protection From H.I.V. in Trial of Young African Women

No incident HIV acquisitions were observed in the LEN group

a Overall n: background HIV incidence group 8094, LEN 2134, F/TAF 2136, F/TDF 1068. b 95% CIs: background HIV incidence group 1.82, 3.19, LEN 0, 0.19, F/TAF 1.44, 2.76. F/TDF 0.96, 2.74
PY, person-years

1. Bekker LG, et al. AIDS 2024, Oral SS0407. 2. Bekker LG, et al. N Engl J Med. 2024;10.1056/NEJMoa2407001

LEN for Prevention: Highly Efficacious

PURPOSE 2

Gilead's Twice-Yearly Lenacapavir for HIV Prevention Reduced HIV Infections by 96% and Demonstrated Superiority to Daily Truvada® in Second Pivotal Phase 3 Trial

– 99.9% of Participants Did Not Acquire HIV Infection in the Lenacapavir Group, with 2 Incident Cases Among 2,180 Participants –

– PURPOSE 2 Trial Results for Cisgender Men and Gender-Diverse People Add to the Body of Evidence for the Investigational Use of Lenacapavir for HIV Prevention –

– Gilead Stopped the Blinded Phase of the Trial at Interim Analysis and Will Offer Open-Label Lenacapavir to All Participants –

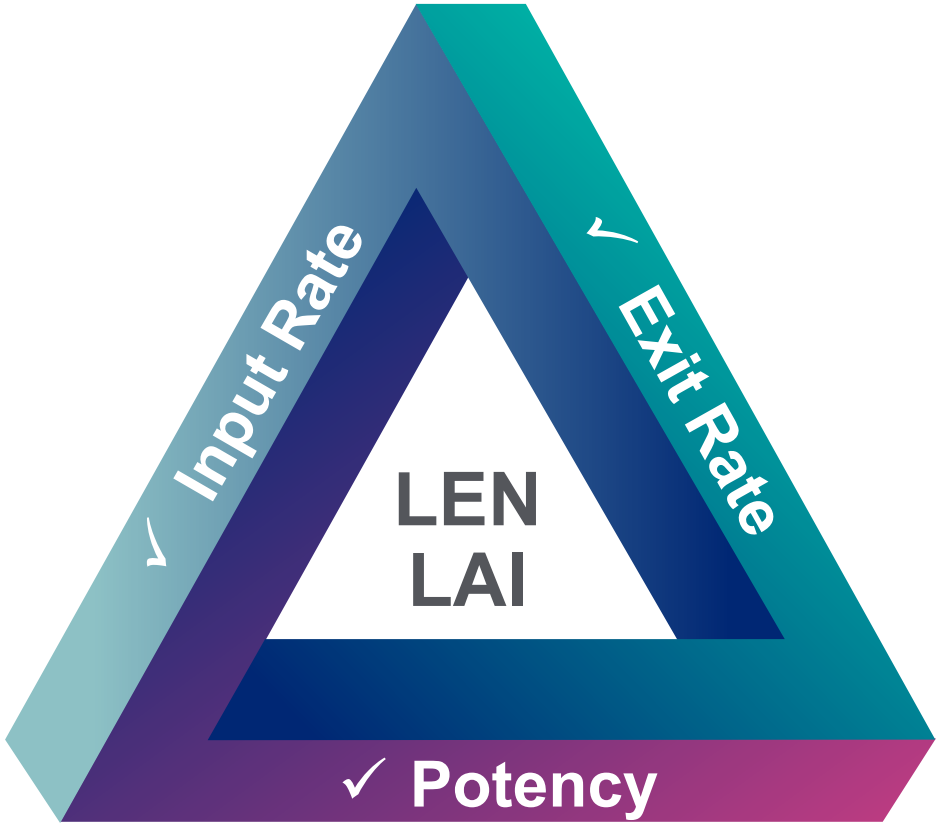
September 12, 2024 08:30 AM Eastern Daylight Time

FOSTER CITY, Calif.--(BUSINESS WIRE)--Gilead Sciences, Inc. (Nasdaq: GILD) today announced the results of an interim analysis from a second pivotal Phase 3 clinical trial investigating the use of the company's twice-yearly injectable HIV-1 capsid inhibitor, lenacapavir. Lenacapavir reduced HIV infections by 96% compared to background HIV incidence (bHIV). There were 2 incident cases among 2,180 participants, corresponding to 99.9% of participants not acquiring HIV infection in the lenacapavir group. Twice-yearly lenacapavir also demonstrated superiority to once-daily Truvada® (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg; F/TDF).

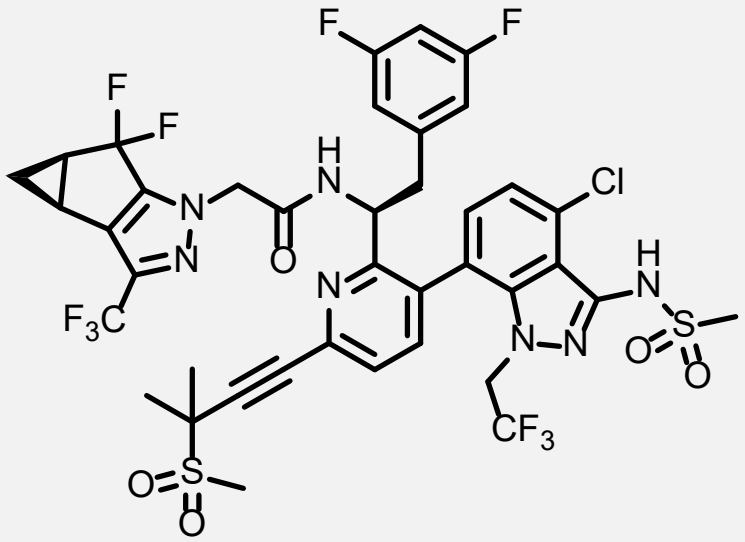
Business Wire, 12th Sep 2024

Conclusions

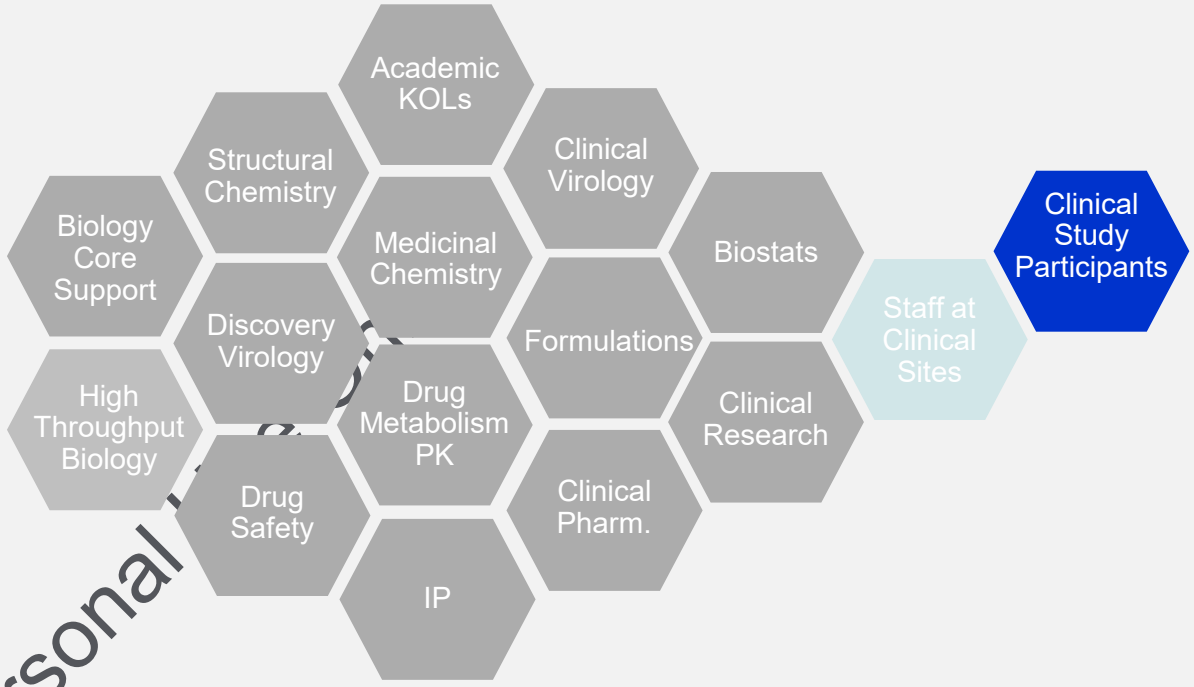
- ☑ Lenacapavir has optimal properties for long acting antiretroviral agent
- ☑ Picomolar inhibitor of HIV capsid function
- ☑ Highly effective against a broad range of HIV-1 strains
- ☑ Displays sustained drug release following a single SC administration without any unintended rapid drug release
- ☑ Well tolerated following single SC administration



Thank you



Lenacapavir



- Gilead research & development teams and KOLs
- Clinical trial participants & study monitors

Questions/Comments – raju.subramanian@gilead.com

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