GILEAD
Creating Possible

A Physiologically Pharmacokinetic Model Based Approach for Translation of Long-acting Lenacapavir

February 15th 2023

Outline

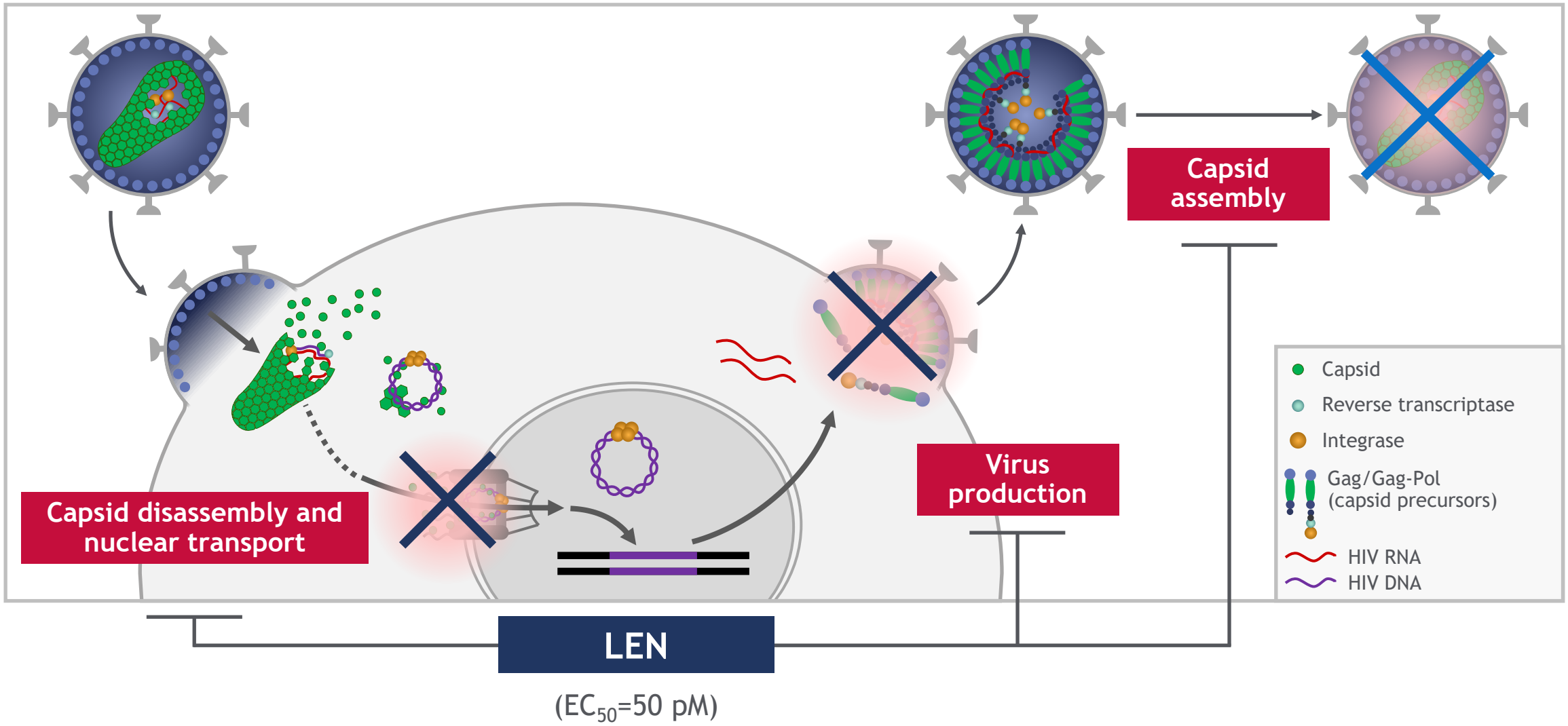
1. Introduction
2. Mechanism of Action
3. Clinical Regimen
4. PBPK model
5. Conclusions

Introduction

- Lenacapavir (LEN)—a potent, first-in-class capsid inhibitor of HIV-1 is approved for the treatment of HIV-1 infection in combination with other antiretrovirals for heavily treatment-experienced (HTE) adults[1]. Additionally, LEN is currently in development for the prevention of HIV-1 infection.
- In ongoing Phase 2/3 studies, people with HIV-1 received 2 weeks of oral LEN loading (600 mg on Days 1 and 2, and 300 mg on Day 8) followed by 927 mg SC Q6M starting from Day 15.
- LEN exhibits low solubility and permeability, making it a suitable candidate for developing as a long-acting injection.
- Following SC administration, LEN is absorbed slowly over months, with a time to maximal concentration (T_{max}) of 77-84 days and an apparent half-life of 10-12 weeks.
- The SC LEN Q6M formulation is comprised of LEN sodium, polyethylene glycol (PEG) 300, and water for injection.
- In vitro, nonclinical, and clinical data suggest that on SC injection of the LEN Q6M formulation, the drug is initially expected to be in solution; however, due to low aqueous solubility, as the vehicle and excipients (PEG and water) are absorbed, the drug is assumed to form a solid depot; subsequently, the solid depot slowly dissolves over time, where the rate is driven by the solubility and intrinsic dissolution rate of LEN.

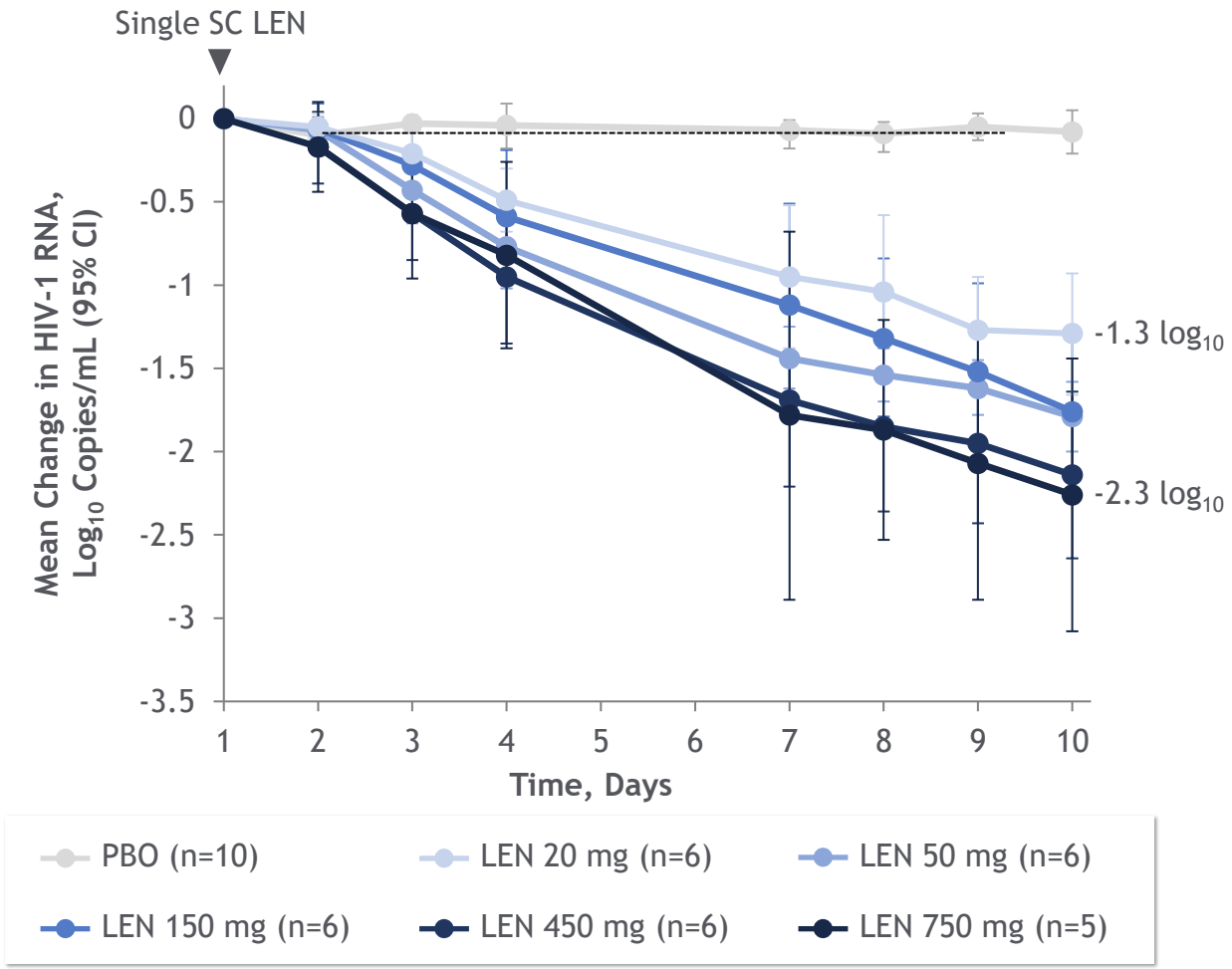
[1] Dvory-Sobol H, Shaik N, Callebaut C, Rhee MS. Lenacapavir: a first-in-class HIV-1 capsid inhibitor. Curr Opin HIV AIDS. 2022 Jan 1;17(1):15-21.

LEN: First-in-class HIV Capsid Inhibitor



EC_{50}, half maximal effective concentration.

Lenacapavir Demonstrates Robust HIV Load Reduction



Daar E et al. CROI 2020

PBPK Modeling Can Address Challenges of Long-acting Drug Development

- Development of long-acting injectables (LAIs) like LEN is time and resource intensive
- LEN SC demonstrates flip-flop kinetics
- Establishing translation between nonclinical and clinical data for LAIs through PBPK modeling can expedite development
  - PK profile of LAIs is largely determined by the release characteristics of the active ingredient resulting in flip-flop kinetics. PBPK model is useful for modeling absorption differences associated with LAIs [1]
  - Differences in the physiological response of tissues at the depot site and their effects on the drug release profile can be captured more robustly with a PBPK model

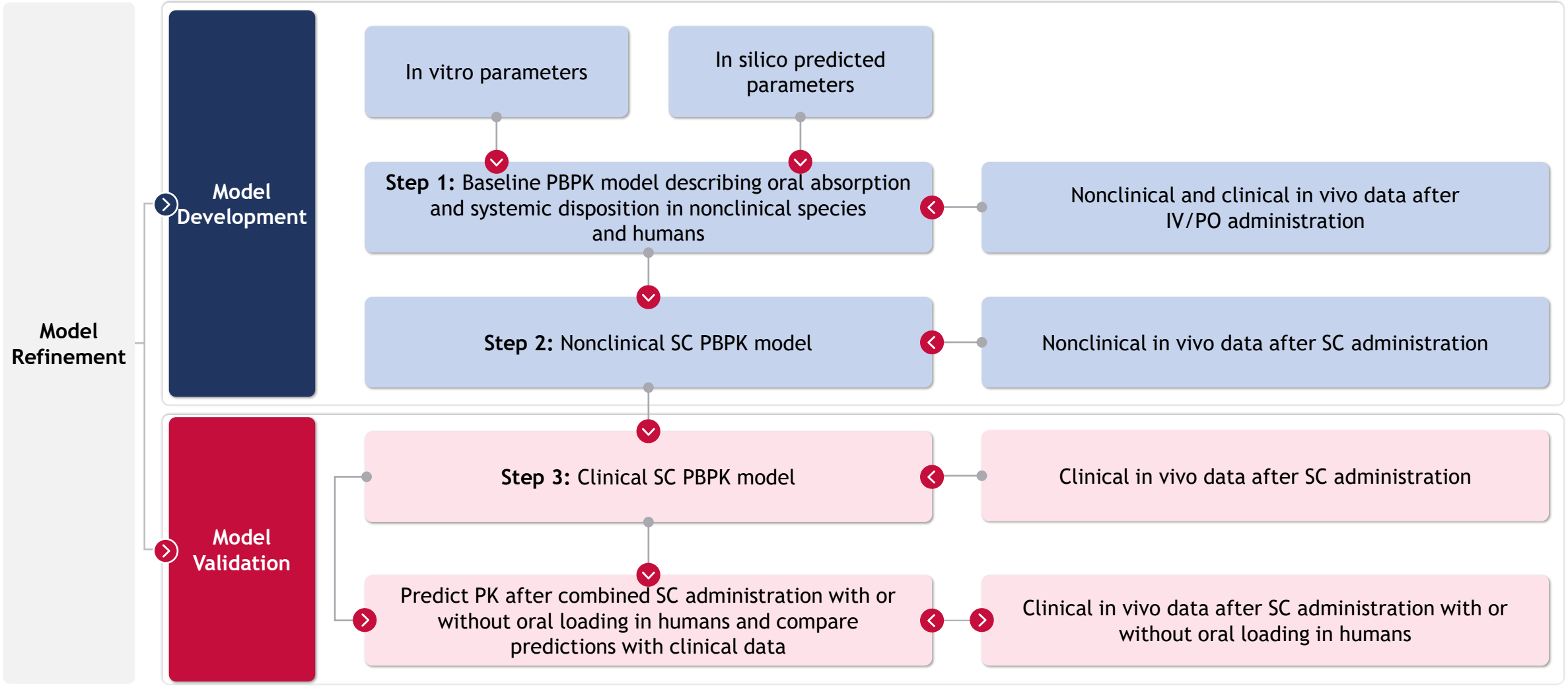
[1] Lukacova V. What does it take to develop a PBPK model that mimics in vivo behavior of LAIs? LAI Conference [Presentation]. 2020

PBPK Model Development for Lenacapavir

Objectives

- To describe the characteristics for nonclinical and clinical LEN PK data
- Establish translation across species
- Simulate LEN PK across various formulations and routes of administration

PBPK Model Development and Validation Methodology

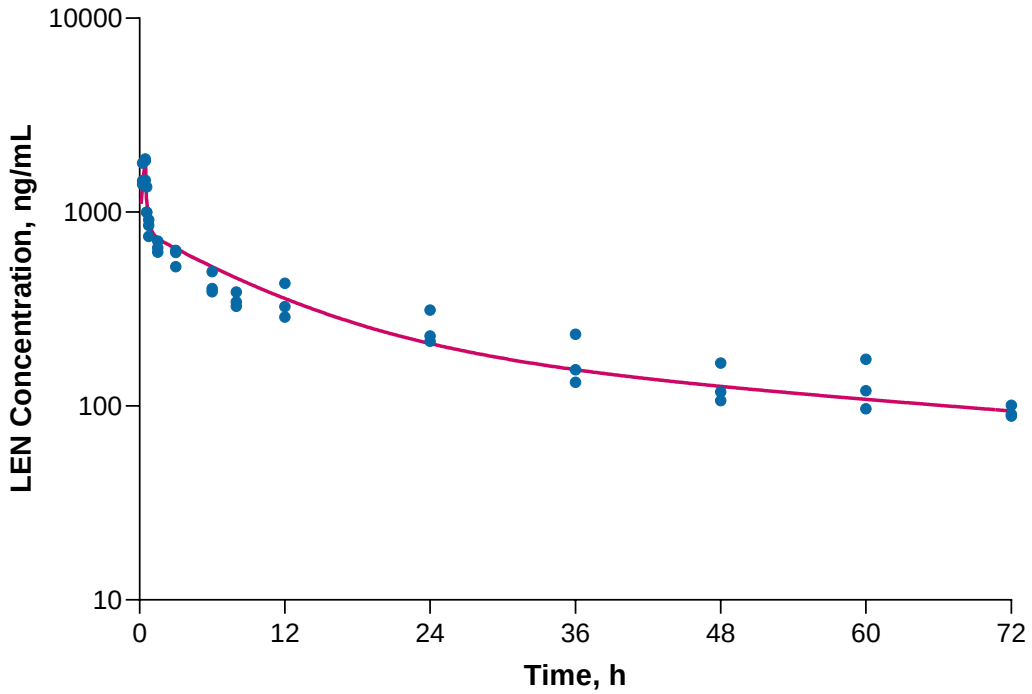


Methods

- PBPK models were developed in GastroPlus® using available rat and human intravenous (IV) LEN data. Subsequently, to describe LEN absorption following SC administration, a combination of solution (minor fraction; phase 1) and solid particles representing precipitate (major fraction; phase 2) were used to model LEN depot formation. The dissolution of precipitate was modeled via fitted Weibull function.
- The rat SC data was used to fit the Weibull parameters and the fitted parameter values were subsequently used to predict the precipitate dissolution in human and compared with the observed human SC data for multiple dose levels.
- The depot volume in human was estimated from depot volume in rat by accounting for differences in injection volumes.

Model Performance- PBPK Model Adequately Describes Lenacapavir PK Following IV administration in Rats

Overlay of Observed vs PBPK Model-Simulated Plasma Concentrations[a]



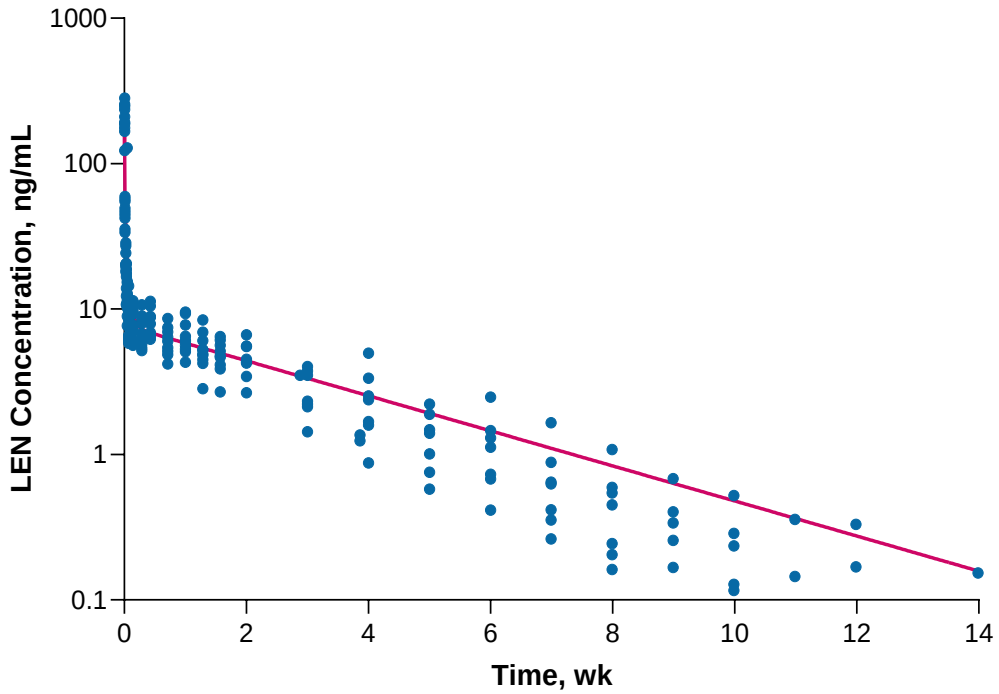
Observed and Model-Simulated PK Parameters for 1 mg/kg IV Dose

Mean Parameter	Observed	Simulated
C_{max}, nM	1,783	1,945
AUC_{inf}, h·nM	22,867	25,787

[a]*Blue circles* represent observed plasma concentrations; *red solid line* represents model-simulated plasma concentration.
AUC_{inf} = area under curve from time 0 to infinity; C_{max} = maximal concentration; SD = standard deviation.
nM to ng/mL conversion factor =0.9683

Model Performance Using LEN IV data in Healthy Participants

Overlay of Observed vs PBPK Model-Simulated Plasma Concentrations[a]



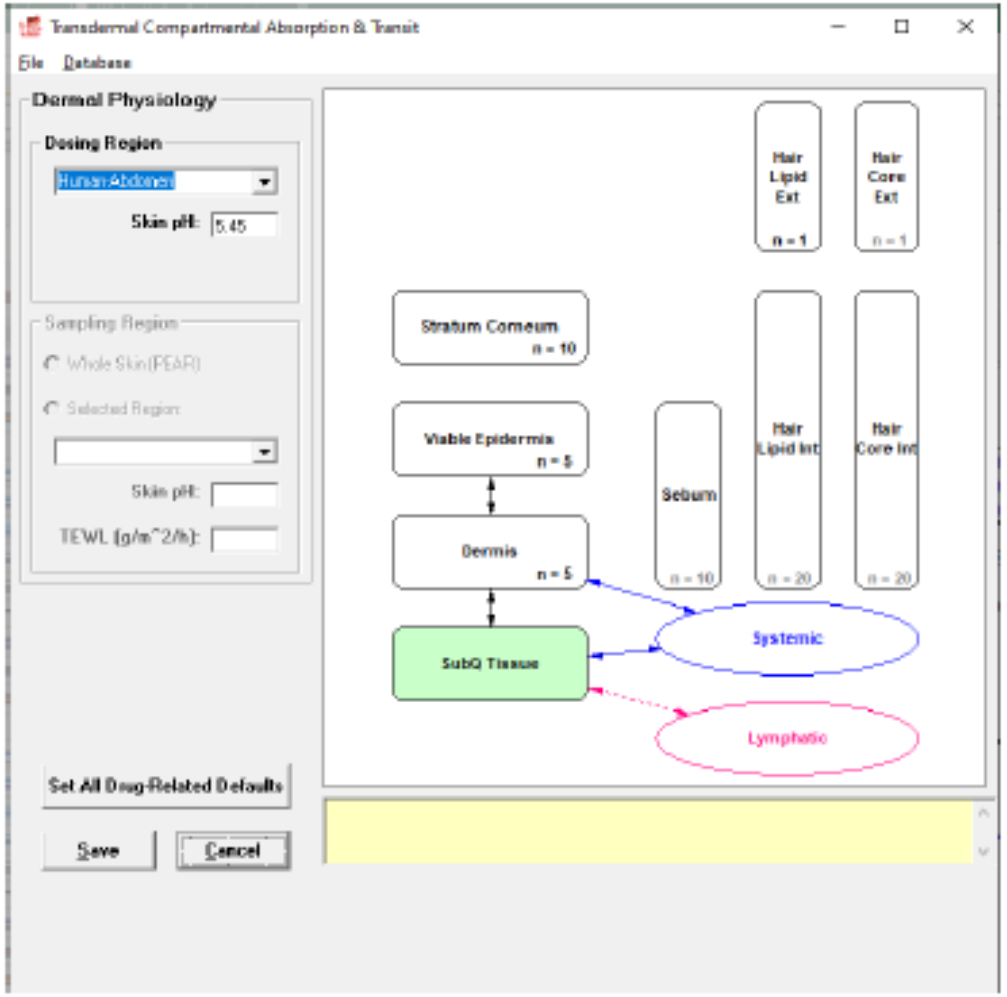
Observed and Model-Simulated PK Parameters

Dose	10 mg	20 mg	10 mg	20 mg
Parameter	Observed		Simulated	
C_{max}, ng/mL	162	208	119	213
AUC_{inf}, h·ng/mL	2,978	4,616	2,601	5,183

[a]*Blue circles* represent observed plasma concentrations and *red solid line* represents model-simulated plasma concentration. NCA parameters from human LEN IV study utilized

PBPK Model Mixed Multiple Dosing for SC Administration

Subcutaneous Transdermal Compartmental Absorption and Transit Model



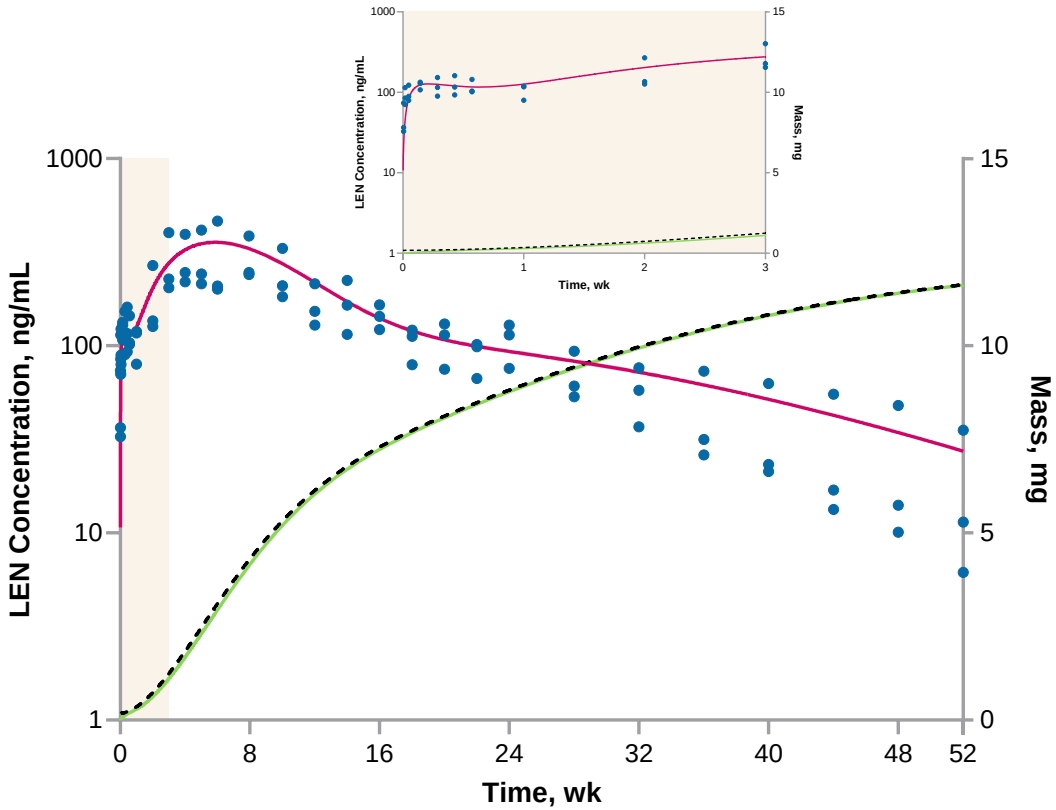
Equation 1. Triple Weibull Equation

$$\%\,DR = Max * \left(1 - f_1 exp\left[\frac{-(t-T)^{b1}}{A_1}\right] - f_2 exp\left[\frac{-(t-T)^{b2}}{A_2}\right] - f_3 exp\left[\frac{-(t-T)^{b3}}{A_3}\right]\right)$$

A_1, A_2, A_3= time scale factors; b_1, b_2, b_3= shape factors ; DR= drug release; f_1, f_2, f_3= release fractions; max=maximum release; T= time lag

Model Performance Using LEN SC data in Rats

Overlay of Observed vs PBPK Model-Simulated Plasma Concentrations[a] for 50 mg/kg dose



[a]Plots represent sodium salt (NaS) 8.7% ethanol alcohol (EtOH) formulation; *red solid lines* represent model-simulated plasma concentrations, *blue circles* represent observed plasma concentrations, *black dashed lines* represent model-simulated amount dissolved, *green lines* represent model-simulated total amount entering in systemic circulation, and *inset* represents first 3 wk of LEN plasma concentration profile, focusing on initial solution absorption.

Model Performance for LEN SC data in Rats

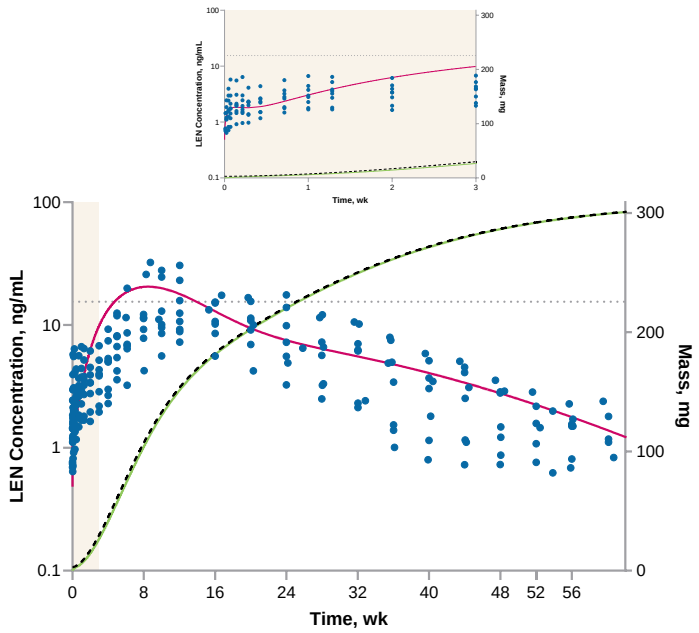
Observed vs Model-Simulated PK Parameters for 50 mg/kg dose

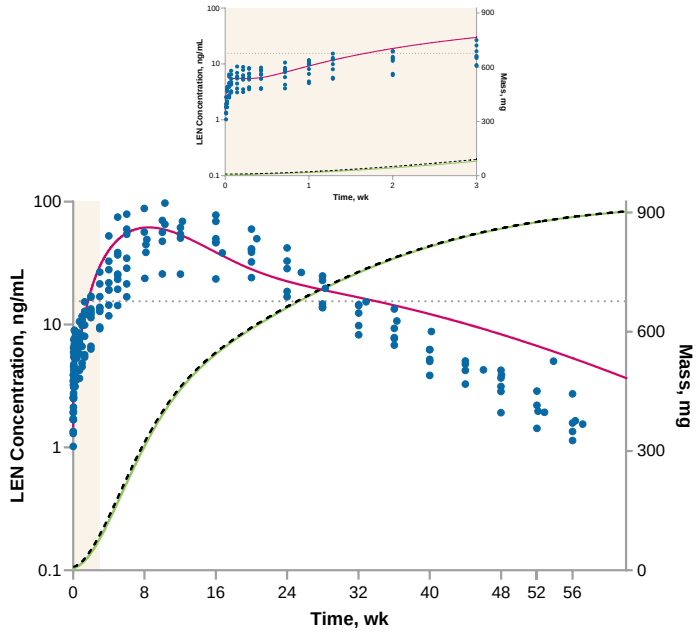
Parameter	Observed				Simulated			
	NaS 8.7% EtOH[b]	NaS 8.7% EtOH + 14% Polox	NaS 68% PEG	NaS 68% PEG + 9.53% Polox	NaS 8.7% EtOH	NaS 8.7% EtOH + 14% Polox	NaS 68% PEG	NaS 68% PEG + 9.53% Polox
C_{max}, ng/mL	317	351	182	247	357	354	208	239
AUC_{inf}, h·ng/mL	988,000	873,000	829,000	728,000	1,170,000	1,170,000	1,320,000	1,320,000

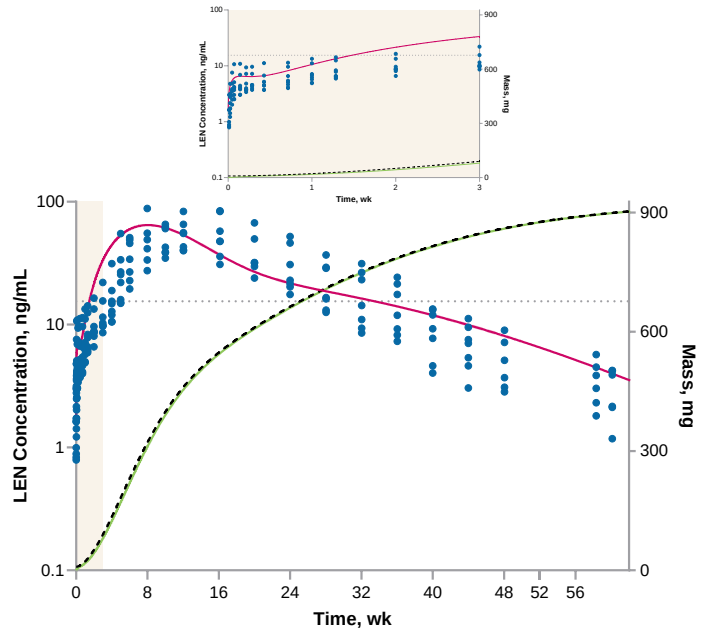
Model Performance for LEN SC data in Healthy Participants

Overlay of Observed vs PBPK Model-Simulated LEN Plasma Concentrations[a]

309 mg (1 x 1 mL) NaS Formulation	927 mg (3 x 1 mL) NaS Formulation	927 mg (2 x 1.5 mL) NaS Formulation







[a]*Blue circles* represent observed plasma concentrations, *red solid line* represents model-simulated plasma concentration, *black dashed lines* represent model-simulated amounts dissolved, *green lines* represent model-simulated total amounts entering in systemic circulation, and *insets* represent first 3 wk of LEN plasma concentration profiles, focusing on initial solution absorption.

Model Performance for LEN SC data in Healthy Participants

Observed vs Model-Simulated PK Parameters

Parameter	Observed			Simulated		
	309 mg (1 x 1 mL)	927 mg (3 x 1 mL)	927 mg (2 x 1.5 mL)	309 mg (1 x 1 mL)	927 mg (3 x 1 mL)	927 mg (2 x 1.5 mL)
C_{max}, ng/mL	17.7	67	61	21	62	65
AUC_{inf}, h·ng/mL	65,810	198,000	225,000	80,230	241,000	242,000

- Scaling of fitted rat parameters to humans allowed capturing of human LEN SC plasma concentration profiles at multiple dose levels; the solution fraction was maintained at ~1% and solid fraction at 99% across dose levels; the model described the human LEN plasma concentration data well
- The ratio between observed and simulated human SC exposures ranged between 0.93 and 1.19, and 1.08 and 1.23 for C_{max} and AUC_{inf}, respectively

Conclusions

A PBPK model with mixed multiple dosing containing solution fraction, as well as solid particle fraction, adequately described rat and human PK profiles of LEN across multiple doses and formulations following IV and SC administration

PBPK could be leveraged to predict and support PK characterization of LEN in humans following administration of different formulations using the release profiles obtained in nonclinical species

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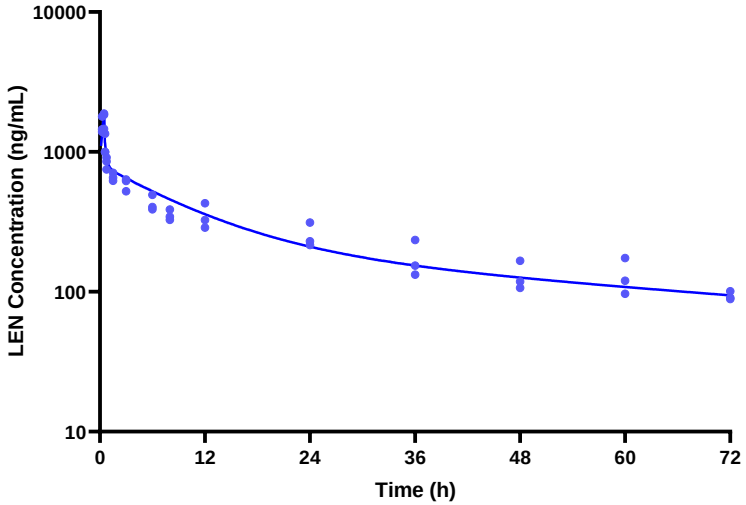
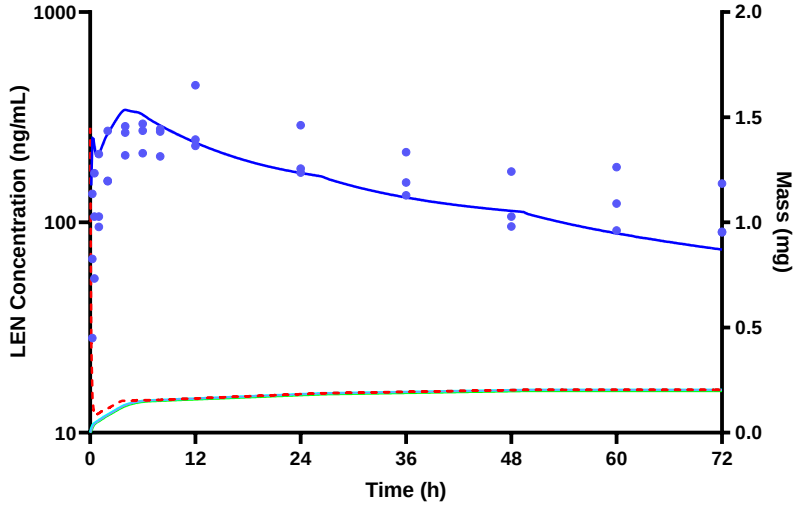
THANK YOU

LEN PBPK Model: Rat IV & PO



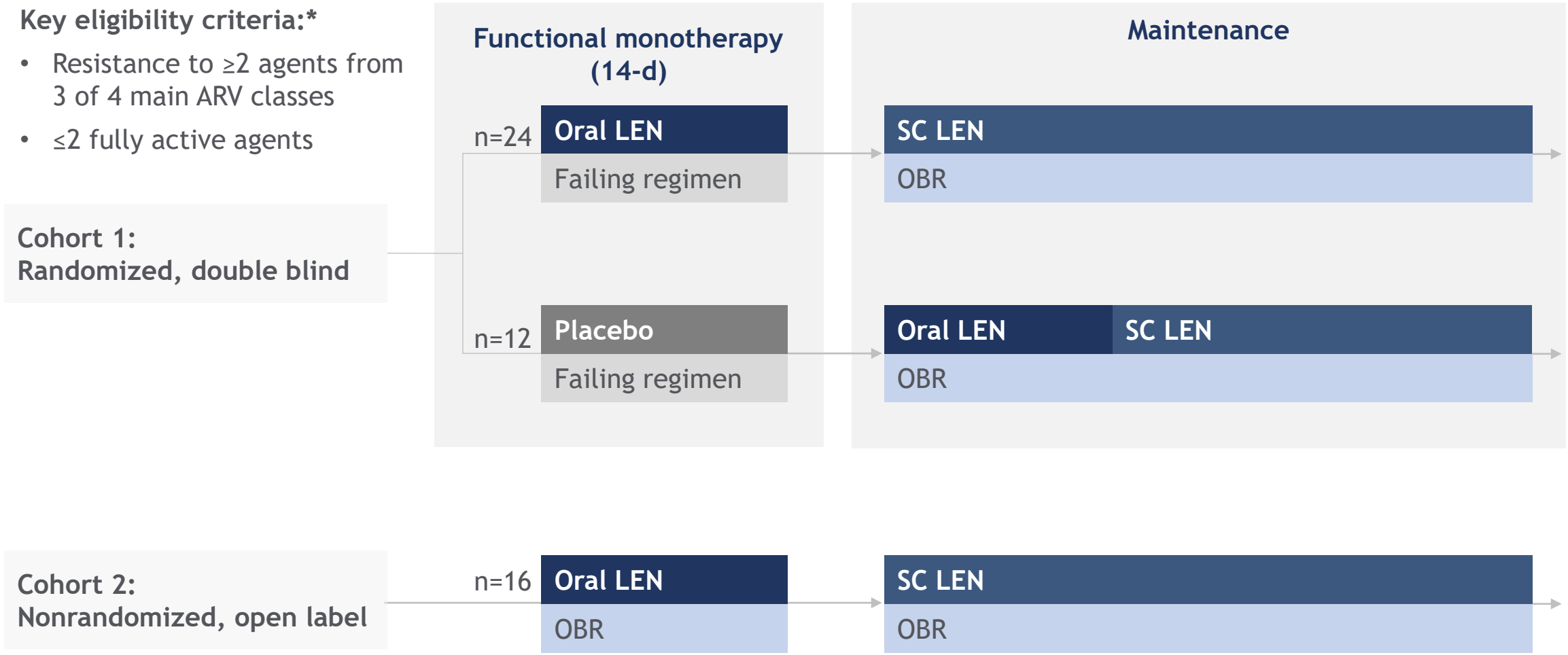


Parameter	Route of Administration			
	Observed		Simulated	
	IV Infusion	Oral	IV Infusion	Oral
Dose (mg/kg)	1	5	1	5
T_{max} (h)	0.48 ± 0.00	10.0 ± 3.5	0.5	4
C_{max} (nM)	1783 ± 238	336 ± 116	1945	354
$AUC_{0\text{-}72h}$ (nM•h)	17533 ± 3182	13467 ± 3927	17123	11567
AUC_{inf} (nM•h)	22867 ± 2011	25200 ± 10221	25787	17422
CL (L/h/kg)	0.045 ± 0.004	ND	0.037	0.037
V_{ss} (L/KG)	2.22 ± 0.56	ND	2.7	2.7
F (%)*	NA	21.7 ± 8.9	NA	13.69

Study Design: Phase 2/3

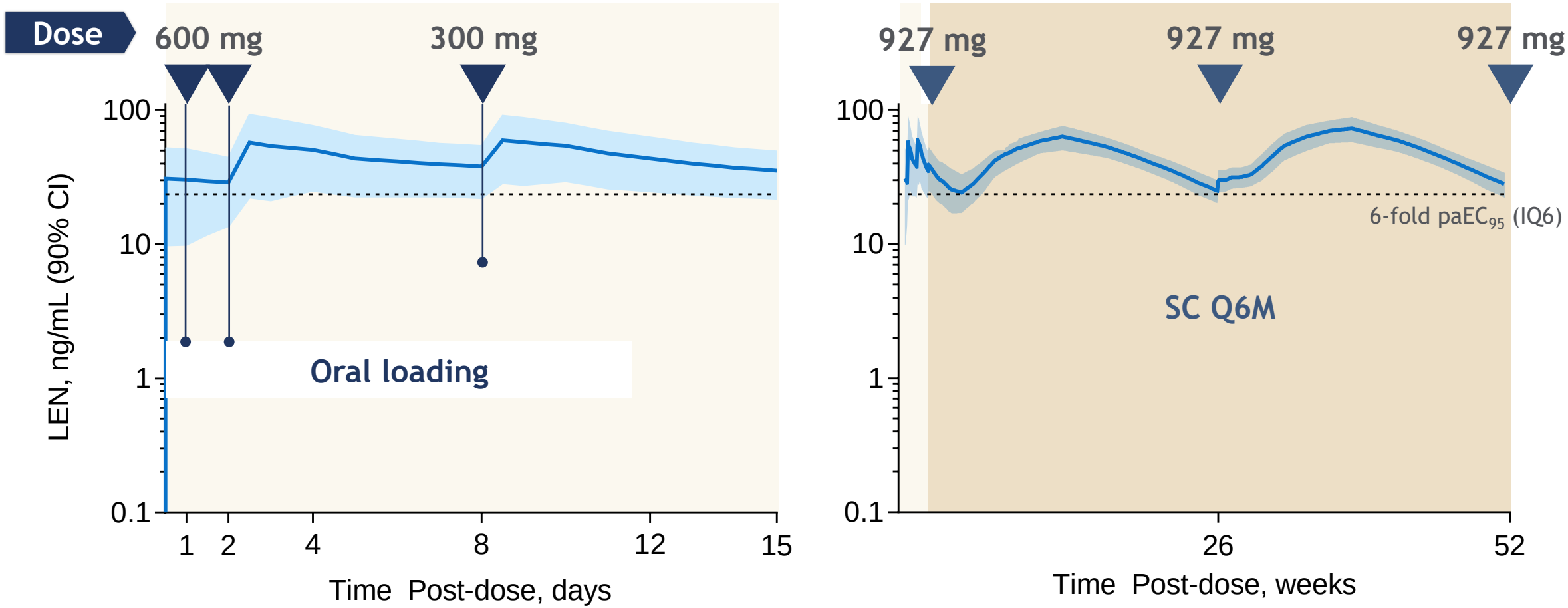
Key eligibility criteria:*

- Resistance to ≥2 agents from 3 of 4 main ARV classes
- ≤2 fully active agents



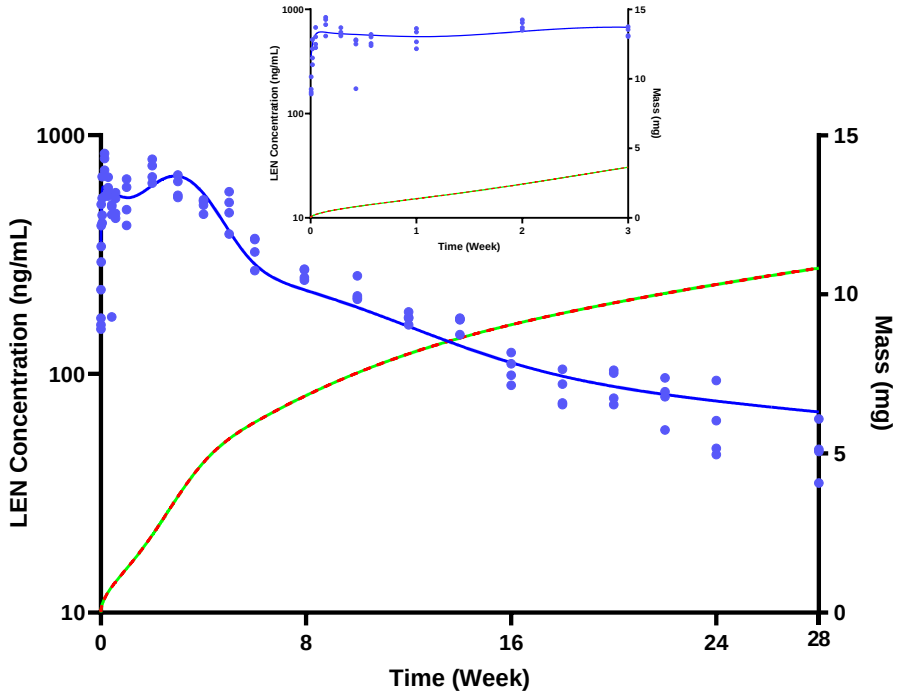
*HIV-1 RNA was repeated prior to randomization to determine the cohort: only participants with <0.5-$\log_{10}$ copies/mL decline and HIV-1 RNA ≥400 copies/mL were enrolled to Cohort 1; otherwise, they were enrolled to Cohort 2.

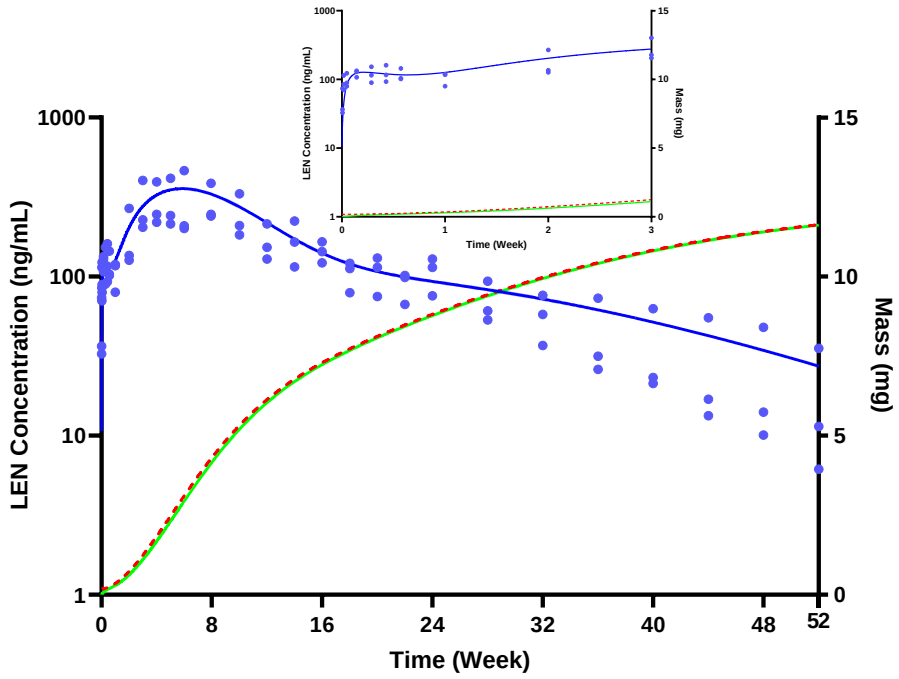
Predicted LEN PK for LEN Clinical Regimen



Begley R, et al. AIDS 2020

Model Performance for LEN SC data in Healthy Participants





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