

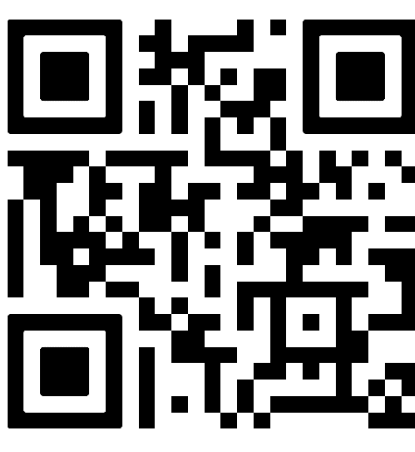
Step-Wise Population Pharmacokinetic Modeling Approach to Characterize Complex Absorption of Lenacapavir Following SC Administration in Healthy Participants

Poster II-050

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Conclusions

- A step-wise approach identified that the 3-compartment PK model with linear elimination adequately described lenacapavir (LEN) concentration data. Subcutaneous absorption was described with three parallel absorption phases with increasing delays.
- The modeling strategies and framework used in this analysis are valuable tools that can be used to describe the disposition and absorption of LEN across different routes of administration and inform regimen selection for LEN.

Background

- Lenacapavir (LEN) is a novel, first-in-class, multistage inhibitor of human immunodeficiency virus type 1 (HIV-1) capsid function, which has potent antiviral activity.^{1,2} LEN is approved at 927 mg subcutaneously every 26 weeks in combination with other antiretroviral therapies for the treatment of multidrug resistant (MDR) HIV-1 infection in heavily treatment experienced (HTE) people with HIV-1 (PWH).^{3,4}
- LEN exhibits low solubility and permeability, making it a suitable candidate for developing as a long-acting injection. Following subcutaneous (SC) administration, LEN is absorbed slowly over months, with a time to maximal concentration of 77-84 days and apparent half-life of 8-12 weeks.^{3,4}
- Due to low aqueous solubility, as the vehicle and excipients (polyethylene glycol 300 and water) are absorbed, LEN is assumed to precipitate as a solid depot; subsequently, the solid depot slowly dissolves over time, where the absorption rate is driven by the solubility and intrinsic dissolution rate of LEN.⁵
- Previously a 2-compartment disposition model was developed to describe LEN PK following IV, oral and SC administration.⁶
- The absorption of LEN is complex and involves multiple parallel phases, which makes characterization of LEN absorption and identification of covariates challenging yet crucial to understand LEN's PK properties.

Objective

- Characterize the complex absorption and disposition of LEN after intravenous (IV) and SC administration in healthy participants using a step-wise modeling approach.

Methods

- The dataset included a total of 42 participants and 1045 quantifiable concentrations pooled from two phase 1 studies in healthy participants of which 18 individuals received a single IV dose of LEN (10 mg or 20 mg) and 24 received SC abdominal injection(s) as a single dose (309 mg or 927 mg) (**Table 1**). Concentrations below the limit of quantification (n=56) were excluded from the analysis.
- To ensure characterization of the absorption and disposition of LEN, given its fast distribution and elimination compared to slower and complex absorption processes, a stepwise modeling approach was implemented (**Figure 1**).
- Weight, age, body mass index, sex, race, and baseline glomerular filtration rate were evaluated as covariates on clearance, volume of distribution and absorption parameters. Inclusion of covariates were based on visual inspection of the data, improvement in model fit, as well as scientific and clinical relevance.
- NONMEM version 7.5 was used to develop the population PK (PopPK) models. Stochastic approximation expectation maximization (SAEM) (with interaction) followed by importance sampling (IMP) estimation methods were used.
- Models were evaluated with goodness of fit diagnostic plots, parameter uncertainty, model stability, and simulation-based visual predictive checks.

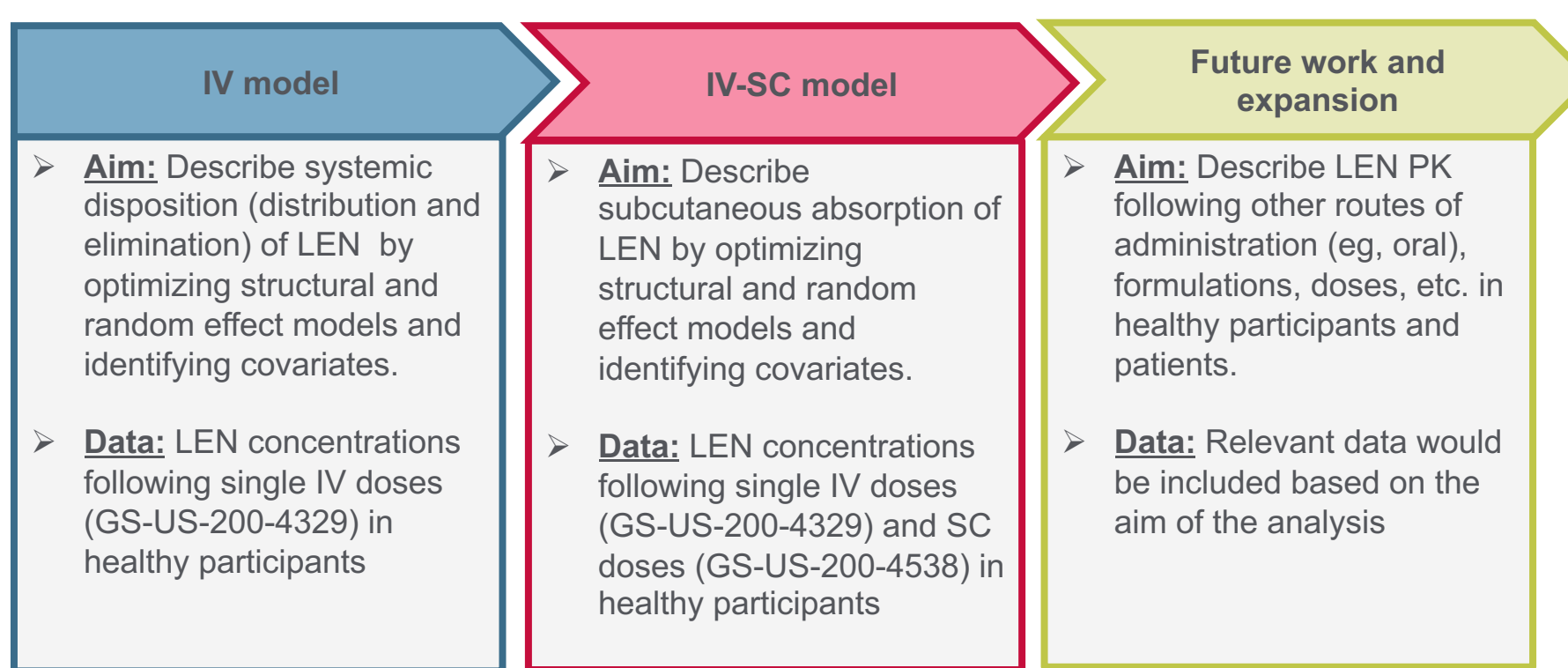
Table 1. Studies Included in PopPK Analysis

Study	Title	Route	N	Dose
GS-US-200-4329	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Metabolism and Excretion of IV LEN in Healthy Subjects	IV	Cohort 1: 8 Cohort 3: 10	Cohort 1: 10 mg Cohort 3: 20 mg
GS-US-200-4538 ¹	A Phase 1 Randomized, Blinded, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Subcutaneous Solutions of LEN in Healthy Subjects	SC	Cohorts 5: 8 Cohorts 6: 8 Cohorts 7: 8	Cohort 5: 309 mg (1 x 1 mL injection) Cohort 6: 927 mg (3 x 1 mL injections) Cohort 7: 927 mg (2 x 1.5 mL injections)

IV=intravenous; N = number of participants; SC = subcutaneous

¹ Only cohorts administering sodium salt (NaS) formulation (309 mg/mL) are listed and included in popPK analysis

Figure 1: Stepwise Approach to Characterize Complex Absorption of Lenacapavir



Results

- Observed data from GS-US-200-4329 and GS-US-200-4538 suggest LEN exhibits slower subcutaneous absorption relative to disposition of LEN when administered intravenously (**Figure 2**).
- LEN disposition following IV administration was adequately described by a 3-compartment model with linear elimination (**Table 2**). Following SC administration of LEN, absorption was adequately described by three parallel transit compartment absorption phases (**Table 3 and Figure 3**).
- The ratio between the disposition PK parameters (CL, Vc, Q1, Q2, Vc, Vp1, and Vp2) estimated in the IV-SC model (**Table 2**) versus the IV model (**Table 1**) were between 0.88 and 1.18. This indicates that the characterization of disposition of LEN remained consistent across both models. Furthermore, absorption parameters appear to be independent of the disposition parameters.
- An initial subcutaneous absorption phase occurs rapidly (completed within the first day) without a lag time, while the second and third absorption phases have delays described by lag times of 10.7 and 37.3 days, respectively. The absorption rate constant for the initial absorption phase was 0.00676/h, second phase was 0.000300/h and third phase was 0.000577/h. Together these three phases led to a median observed time to reach maximum concentration of 84 days (range 35 to 168 days).
- SC bioavailability was estimated as 83.7% over the duration of sampling, with 4.0% of the bioavailable dose accounted for in the initial absorption phase, 41.0% in the second absorption phase, and 55.0% in the third absorption phase.
- Inter-individual variability was estimated for all three absorption rates as well as both lag times.
- No apparent bias was observed in model diagnostic plots and visual predictive checks (**Figures 4-7**).
- Given the homogeneity of the population in this analysis (healthy participants), no additional covariates were visually or statistically identified.

Figure 2: Observed PK profiles of LEN following IV (left) and SC (right) administration

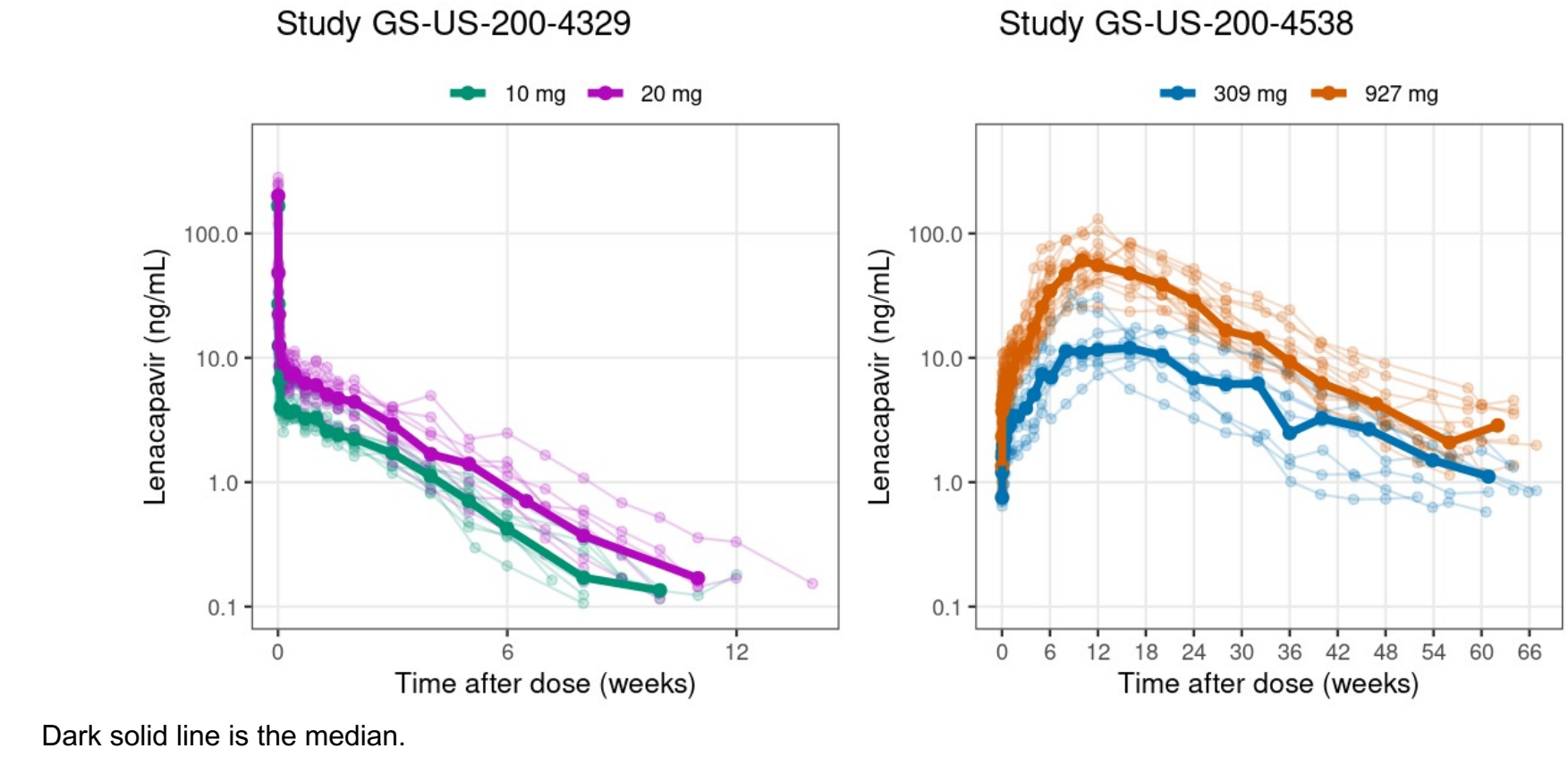


Figure 3: Structural IV-SC Model for Subcutaneous Absorption and Disposition of LEN

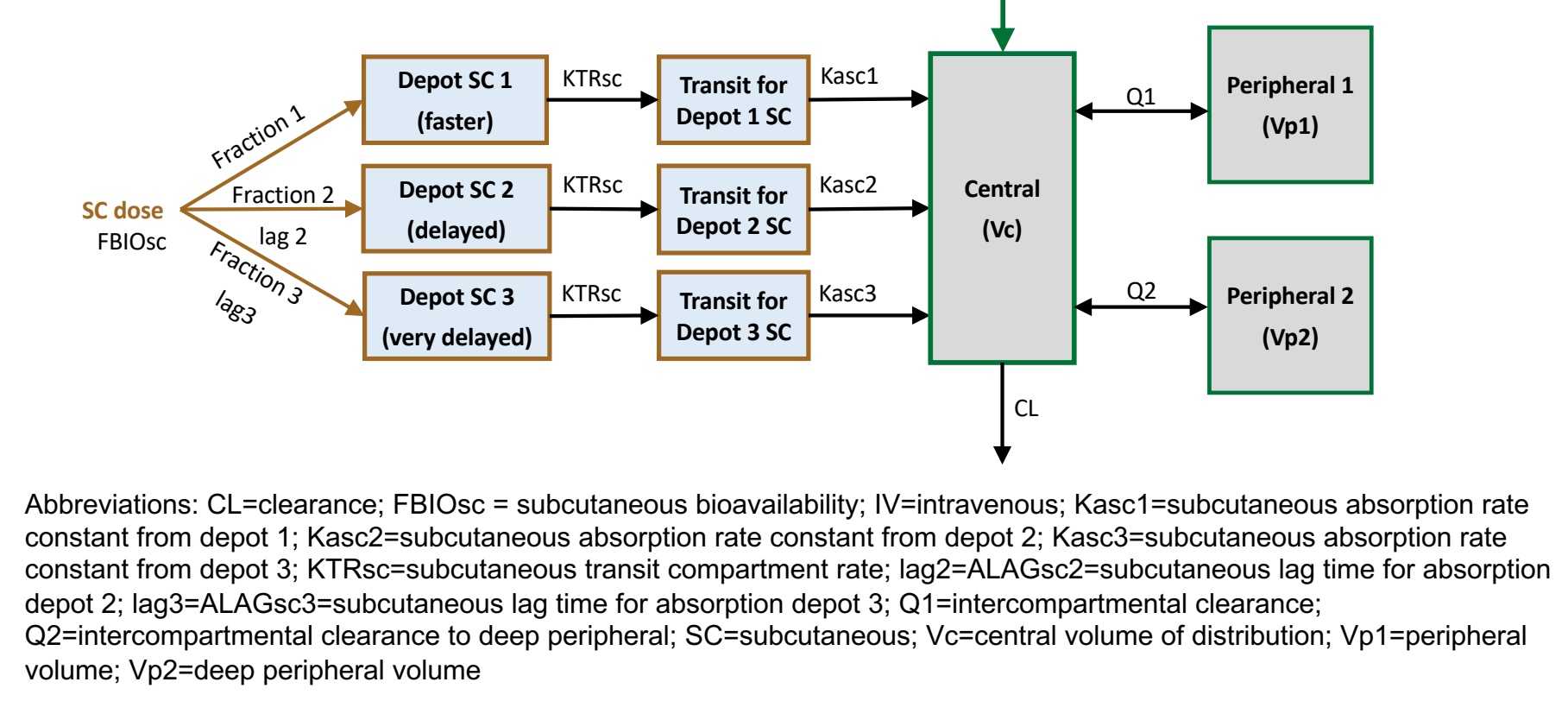


Table 2. Population PK parameter Estimates of LEN following IV administration (IV Model)

Structural Parameters		Estimate	RSE (%)	Shrinkage (%)
CL (L/h)	θ_{11}	4.14	3.86	-
Vp2 (L)	θ_{12}	1569	3.92	-
Q2 (L/h)	θ_{13}	43.2	4.46	-
Vc (L)	θ_{14}	3.94	29.3	-
Vp1 (L)	θ_{15}	45.7	6.24	-
Q1 (L/h)	θ_{16}	44.9	8.03	-
Variance Parameters				
IV on CL	$\hat{\Omega}_{(1,1)}$	0.0250 [CV%=15.9]	-	-
IV on Vp2	$\hat{\Omega}_{(2,2)}$	0.0250 [CV%=15.9]	-	-
IV on Q2	$\hat{\Omega}_{(3,3)}$	0.0250 [CV%=15.9]	-	-
IV on Vc	$\hat{\Omega}_{(4,4)}$	0.0250 [CV%=15.9]	-	-
IV on Vp1	$\hat{\Omega}_{(5,5)}$	0.0250 [CV%=15.9]	-	-
IV on Q1	$\hat{\Omega}_{(6,6)}$	0.0250 [CV%=15.9]	-	-
Residual Variance				
Proportional error	θ_{17}	0.114	9.69	-
Additive error	θ_{18}	0.0292	25.3	-
IV on proportional error	$\hat{\Omega}_{(7,7)}$	0.113 [CV%=34.6]	40.6	15.6

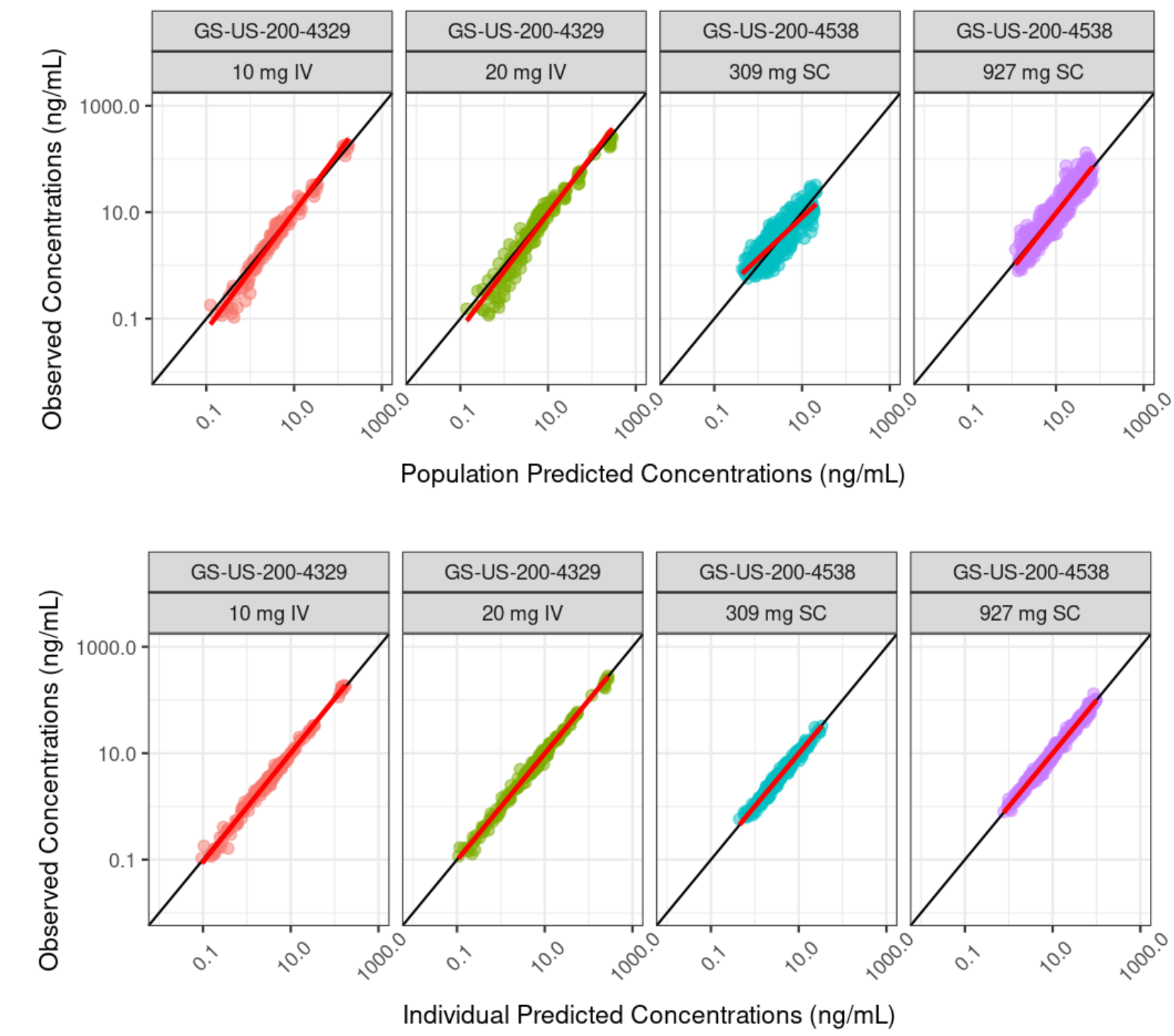
Abbreviations: CV=coefficient of variation; IV=interindividual variability; RSE=relative standard error; SD=standard deviation
CV% of log-normal omegas = $\sqrt{\text{exp}(\text{estimate}) - 1} \times 100$

Table 3: Population PK parameter Estimates of LEN following IV and SC administration (IV-SC Model)

Structural Parameters		Estimate	RSE (%)	Shrinkage (%)
CL (L/h)	θ_{11}	3.64	6.54	-
Vp2 (L)	θ_{12}	1844	3.38	-
Q2 (L/h)	θ_{13}	41.1	5.31	-
Vc (L)	θ_{14}	3.45	26.1	-
Vp1 (L)	θ_{15}	45.1	6.71	-
Q1 (L/h)	θ_{16}	45.1	8.47	-
Absorption Parameters				
Kasc1 (1/h)	θ_{17}	0.00676	21.1	-
Kasc2 (1/h)	θ_{18}	0.000300	7.75	-
Kasc3 (1/h)	θ_{19}	0.000577	12.8	-
KTRsc (1/h)	θ_{20}	0.373	8.97	-
ALAGsc2 (h)	θ_{21}	256	26.0	-
ALAGsc3 (h)	θ_{22}	896	6.98	-
FBIOSc	θ_{23}	0.837	22.3	-
Fr1	θ_{24}	0.0397	11.6	-
Fr3	θ_{25}	0.550	5.20	-
Variance Parameters				
IV on CL	$\hat{\Omega}_{(1,1)}$	0.0250 [CV%=15.9]	-	-
IV on Vp2	$\hat{\Omega}_{(2,2)}$	0.0250 [CV%=15.9]	-	-
IV on Q2	$\hat{\Omega}_{(3,3)}$	0.0250 [CV%=15.9]	-	-
IV on Vc	$\hat{\Omega}_{(4,4)}$	0.0250 [CV%=15.9]	-	-
IV on Vp1	$\hat{\Omega}_{(5,5)}$	0.0250 [CV%=15.9]	-	-
IV on Q1	$\hat{\Omega}_{(6,6)}$	0.0250 [CV%=15.9]	-	-
IV on Kasc1	$\hat{\Omega}_{(7,7)}$	0.189 [CV%=45.6]	74.8	5.44
IV on Kasc2	$\hat{\Omega}_{(8,8)}$	0.105 [CV%=33.3]	73.9	11.6
IV on Kasc3	$\hat{\Omega}_{(9,9)}$	0.192 [CV%=46.0]	107	4.12
IV on KTRsc	$\hat{\Omega}_{(10,10)}$	0.0250 [CV%=15.9]	-	-
IV on ALAGsc2	$\hat{\Omega}_{(11,11)}$	0.264 [CV%=55.0]	114	8.95
IV on ALAGsc3	$\hat{\Omega}_{(12,12)}$	0.0754 [CV%=28.0]	45.6	5.50
IV on FBIOSc	$\hat{\Omega}_{(13,13)}$	0.678 [SD=0.179]	378	22.1
Residual Variance				
Proportional error (Study GS-US-200-4329)	θ_{17}	0.118	8.41	-
Additive error	θ_{18}	0.0286	24.5	-
Effect of GS-US-200-4538 on proportional error	θ_{19}	1.13	9.90	-
IV on proportional error	$\hat{\Omega}_{(14,14)}$	0.0451 [CV%=21.5]	81.0	26.4

Abbreviations: CV=coefficient of variation; IV=interindividual variability; RSE=relative standard error; SD=standard deviation
CV% of log-normal omegas = $\sqrt{\text{exp}(\text{estimate}) - 1} \times 100$

Figure 4: LEN Observations Versus Population and Individual Predictions by Study and Dose for the IV-SC Model



Abbreviations: IV=intravenous; SC=subcutaneous
Observations versus population (top) or individual (bottom) predictions are presented as colored circles. Identity line is presented as a solid black line and linear regression line as a solid red line. Plots are in log-log scale.

Figure 5: Normalized Prediction Distribution Error Diagnostic LEN concentrations

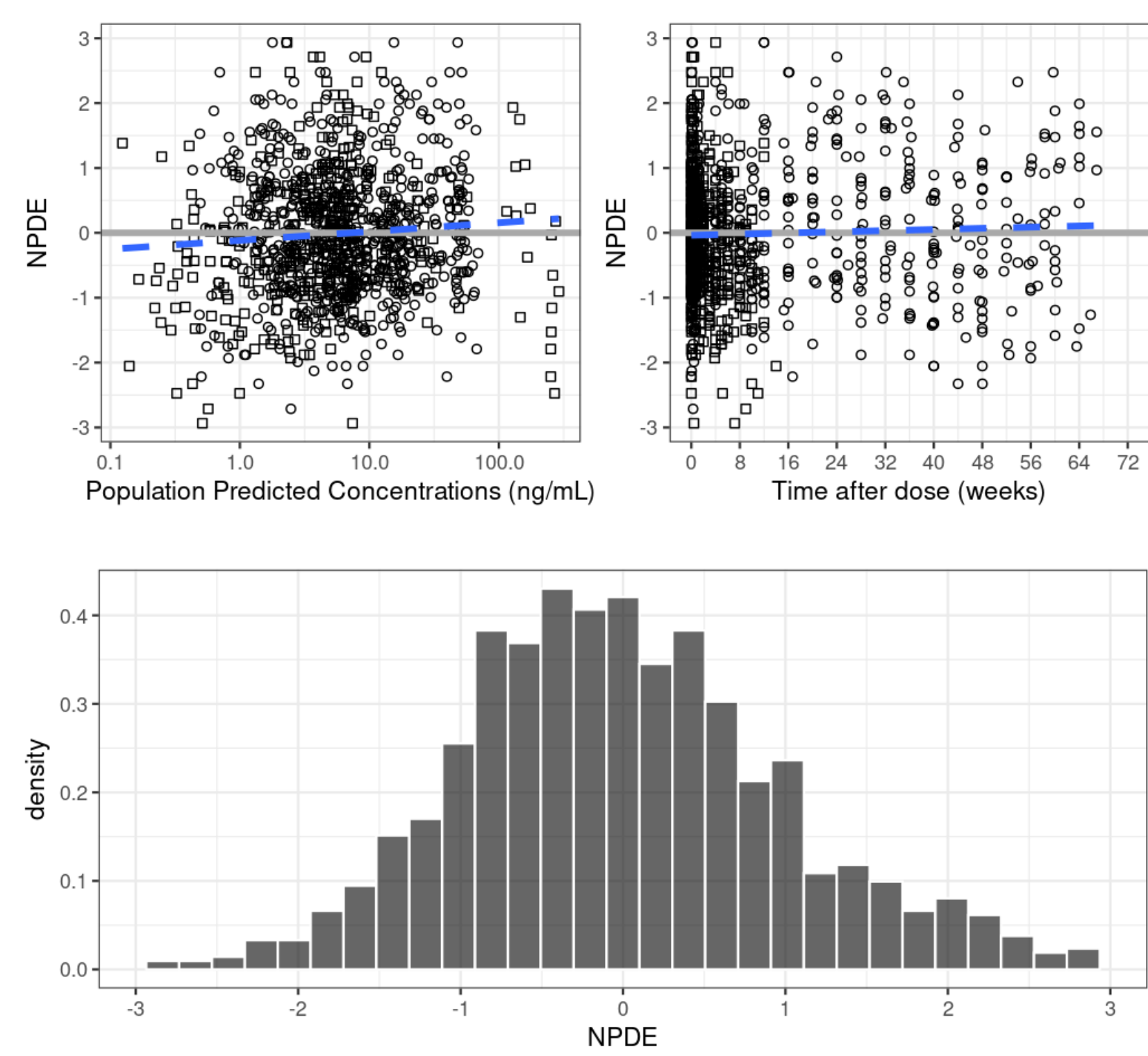
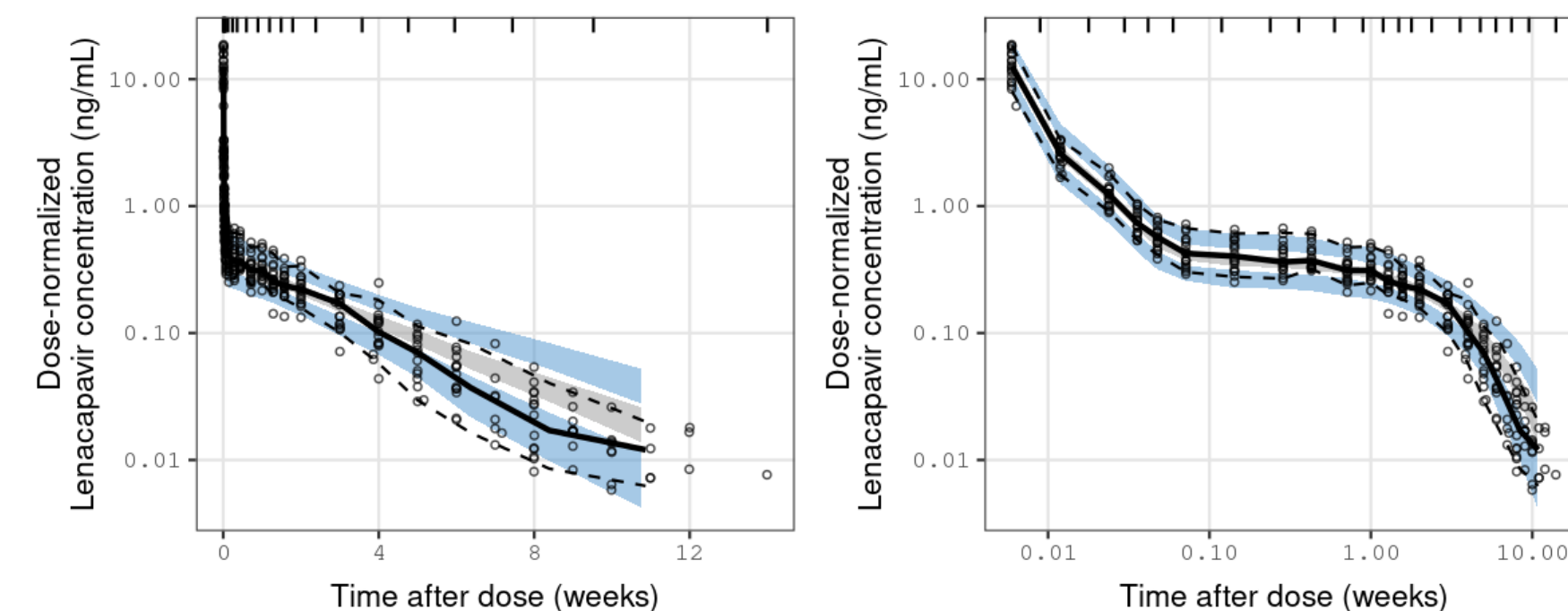
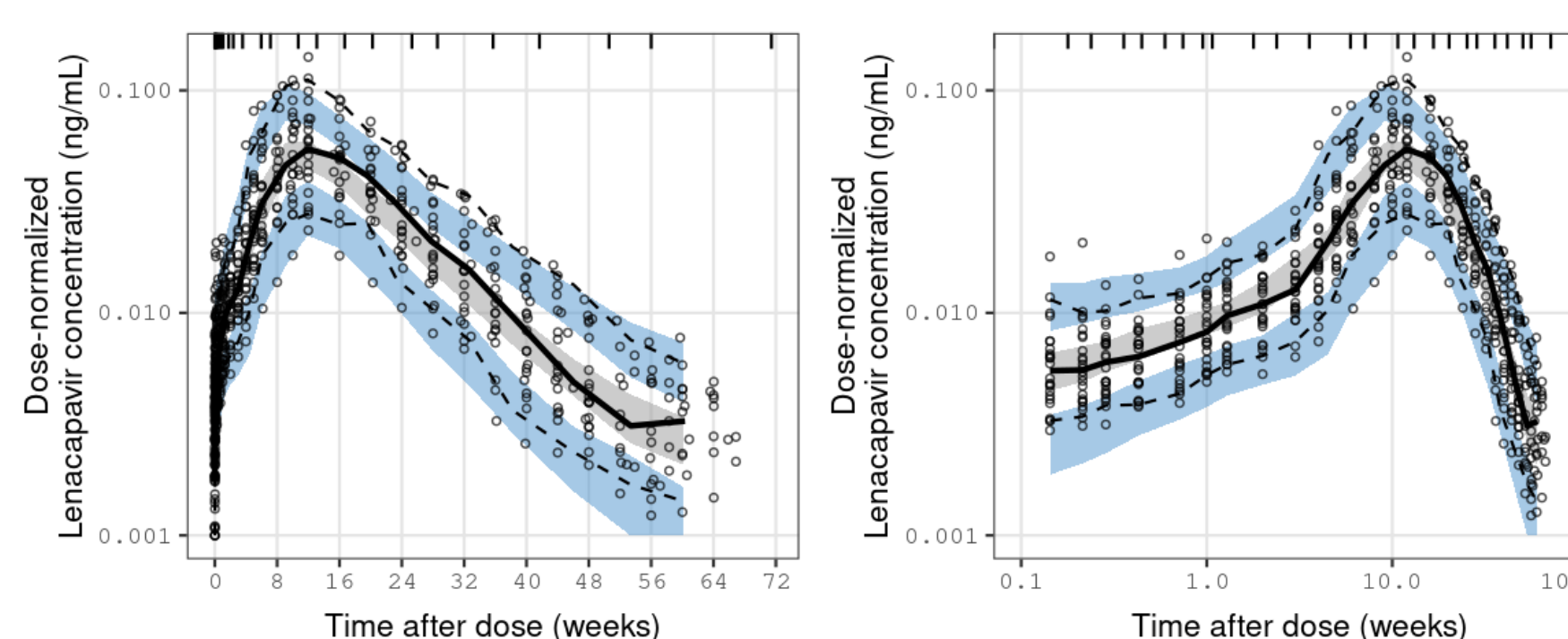


Figure 6: Study GS-US-200-4329 Visual Predictive Checks of LEN Concentrations Following IV Dosing Using the IV-SC Model



Each plot shows the median (solid line) and 5th and 95th percentiles (dashed lines) of observed data and 90% confidence intervals of the median (grey) and 5th (blue) and 95th (blue) percentiles of model predicted simulations (shaded areas). Each circle is an observation. Left plots are in log-linear scale and right plots are in log-log scale. VPCs are dose-normalized.

Figure 7: Study GS-US-200-4538 Visual Predictive Checks of LEN Concentrations Following SC Dosing Using the IV-SC Model



Each plot shows the median (solid line) and 5th and 95th percentiles (dashed lines) of observed data and 90% confidence intervals of the median (grey) and 5th (blue) and 95th (blue) percentiles of model predicted simulations (shaded areas). Each circle is an observation. Left plots are in log-linear scale and right plots are in log-log scale. VPCs are dose-normalized.

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