

Long-Acting Injectables

Formulations intended for prolonged drug release that offer several benefits including improved patient outcomes, yet a limited number of generics are available.

Evaluating model-based extrapolation of exposure for long-acting injectable products: from single- to multiple-dose

BACKGROUND

Lengthy in vivo PK bioequivalence studies hamper generic LAI product availability

- The prolonged release extends the elimination half-life of LAIs, benefiting patients but complicating clinical trial design and regulatory analysis.
- We hypothesized that similar release profiles allow prediction of multiple-dose accumulation from single-dose data via superposition principles.

METHODS

Multiple-dose simulations to externally validate single-dose based models

- Representative datasets were extracted from marketing authorization applications (MAA) dossiers submitted to the Dutch Medicines Evaluation Board (MEB).
- Single-dose models were tested in NONMEM® using Laplacian approximation and M3 method for samples below the limit of quantification (BLQ).
- Multiple-dose simulations ($n=1000$), including lead-in periods and (presumable) steady-state, were performed in RxODE using the single-dose models.
- Simulation results were compared to clinical data using visual and numeric predictive checks. The 95% prediction interval for the geometric mean ratios (GMR) of steady-state PK metrics ($C_{T,ss}$, $C_{max,ss}$, $AUC_{0-T,ss}$) must include 1 to confirm no significant difference from observed data.

“Model-based extrapolation indicates LAI absorption is not different between single and multiple dose studies”

DISCUSSION

Groundwork for model-informed regulatory submissions for generic LAI formulations

- The PK following single-dose administration was best characterized by relatively simple first-order absorption and linear elimination structures (**Table 1**).
- The predictive performance of the single-dose popPK models is satisfactorily (**Figure 1**). Most GMR prediction intervals showed no significant difference between the simulated and observed multiple-dose data (**Figure 2**).
- Future work will explore simulating additional model-based frameworks, such as the switch-study (Gong et al., 2023) for virtual bioequivalence assessments.



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RESULTS

Simulations of multiple-dose studies allow for the prediction of steady-state accumulation

Table 1: Population pharmacokinetic model structures of the long-acting injectables following single-dose administration.

	Model-structure	BSV
Product A	1-compartment double parallel first-order absorption with lagtime on KA_{fast}	CL/F , V_c/F , F_d , KA_{slow}
Product B	2-compartment first-order absorption with lagtime	CL/F , V_c/F
Product C	1-compartment double parallel first-order absorption with lagtime on KA_{slow}	CL/F , V_c/F , F_d , KA_{slow}
Product D	1-compartment first-order absorption	CL/F , V_c/F , KA
Product E	1-compartment first-order absorption	CL/F , V_c/F

Note: CL/F , apparent clearance; V_c/F , apparent volume of distribution in the central compartment; F_d , fraction separating the dose in parallel absorption pathways; KA_{fast} , faster-bound rate of absorption; KA_{slow} , slower-bound rate of absorption. BSV, between-subject variability.

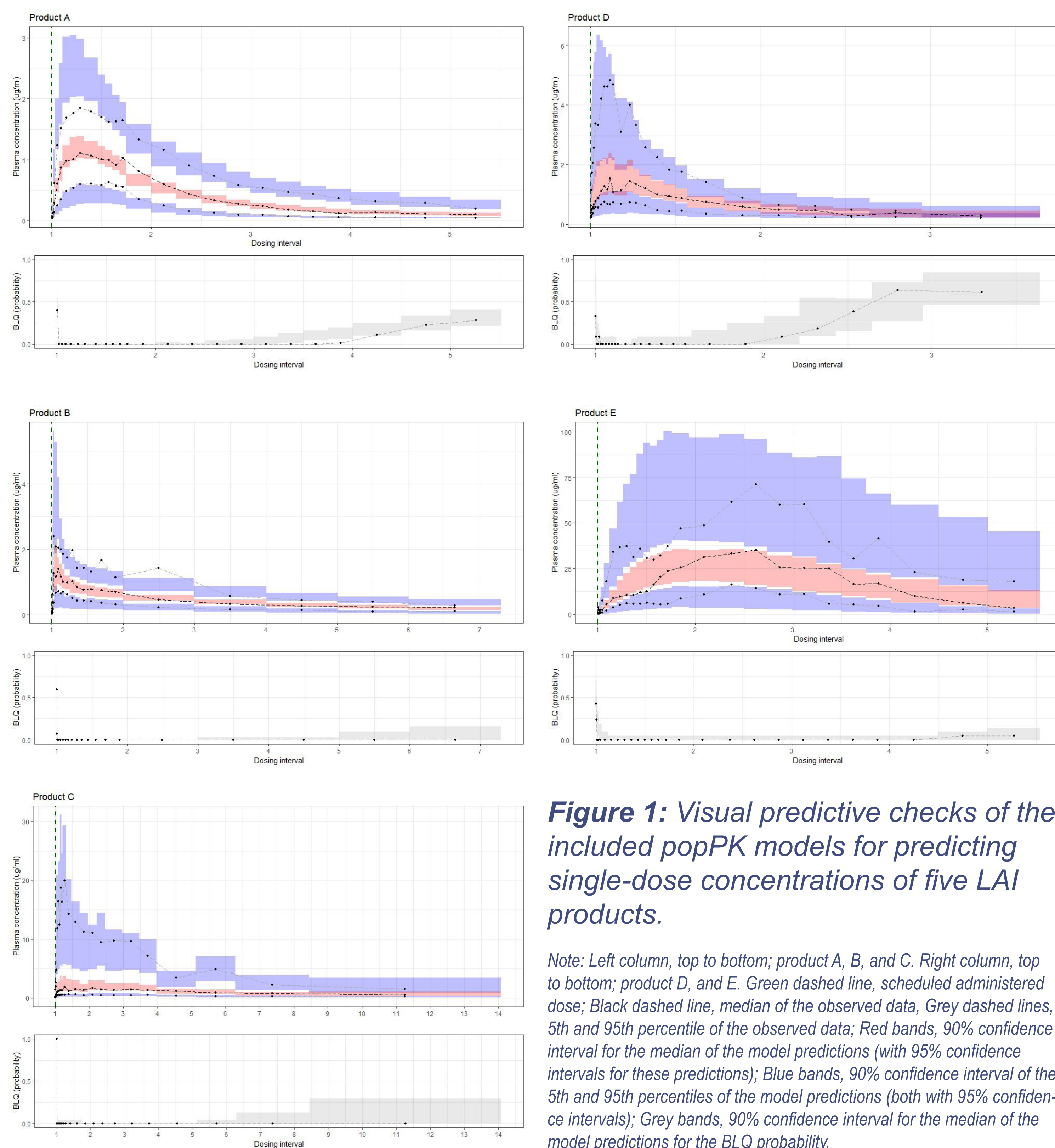


Figure 1: Visual predictive checks of the included popPK models for predicting single-dose concentrations of five LAI products.

Note: Left column, top to bottom; product A, B, and C. Right column, top to bottom; product D, and E. Green dashed line, scheduled administered dose; Black dashed line, median of the observed data; Grey dashed lines, 5th and 95th percentile of the observed data; Red bands, 90% confidence interval for the median of the model predictions (with 95% confidence intervals for these predictions); Blue bands, 90% confidence interval of the 5th and 95th percentiles of the model predictions (both with 95% confidence intervals); Grey bands, 90% confidence interval for the median of the model predictions for the BLQ probability.

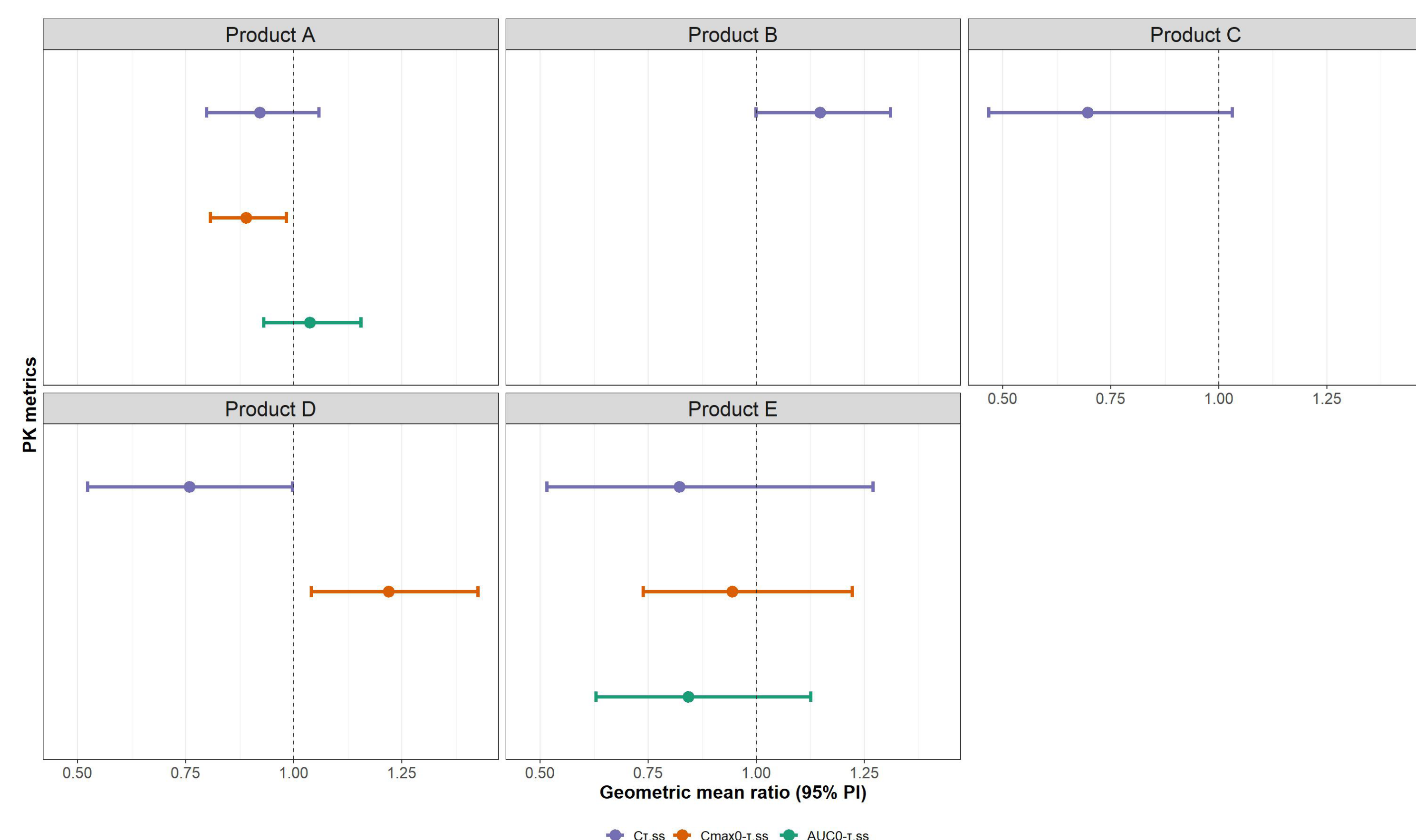


Figure 2: Forest plot of geometric mean ratios with 95% prediction intervals of PK parameters at presumable steady-state scenarios.

Note: $AUC_{0-T,ss}$, area under the plasma concentration curve during a dosing interval; $C_{max,ss}$, maximum concentration; $C_{T,ss}$, concentration reached immediately before the next dose is administered.