

The potential of modelling and simulation as support for generic long-acting injectable (LAI) marketing authorization applications

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.

BACKGROUND

Lengthy in vivo PK bioequivalence studies hamper generic LAI product availability

- EMA guidance requests both a single-dose study and multiple-dose study for the approval of generic LAI products, with the multiple doses having a possibility of a waiver if a low risk of accumulation is shown.
- Complex release characteristics hamper generic development concerning not only formulation challenges, and lifecycle management obstacles, but also lengthy in vivo PK bioequivalence studies.
- Multiple-dose studies are time-consuming and not always feasible because of accompanying safety concerns in healthy volunteers.

METHODS

Single-dose data might be used to simulate multiple-dose scenarios

- A range of single-dose models is tested for 6 different LAI products using non-linear mixed effect modeling (NONMEM®) with the M3 method to handle samples below the limit of quantification (BLQ).
- The model where the model diagnostics aligned best is selected as the final model for multiple-dose simulations. These simulations were performed in R_xODE and compared to the observed data by using VPCs.

PRELIMINARY RESULTS

Statistical evaluations will be used to verify steady-state bioequivalence

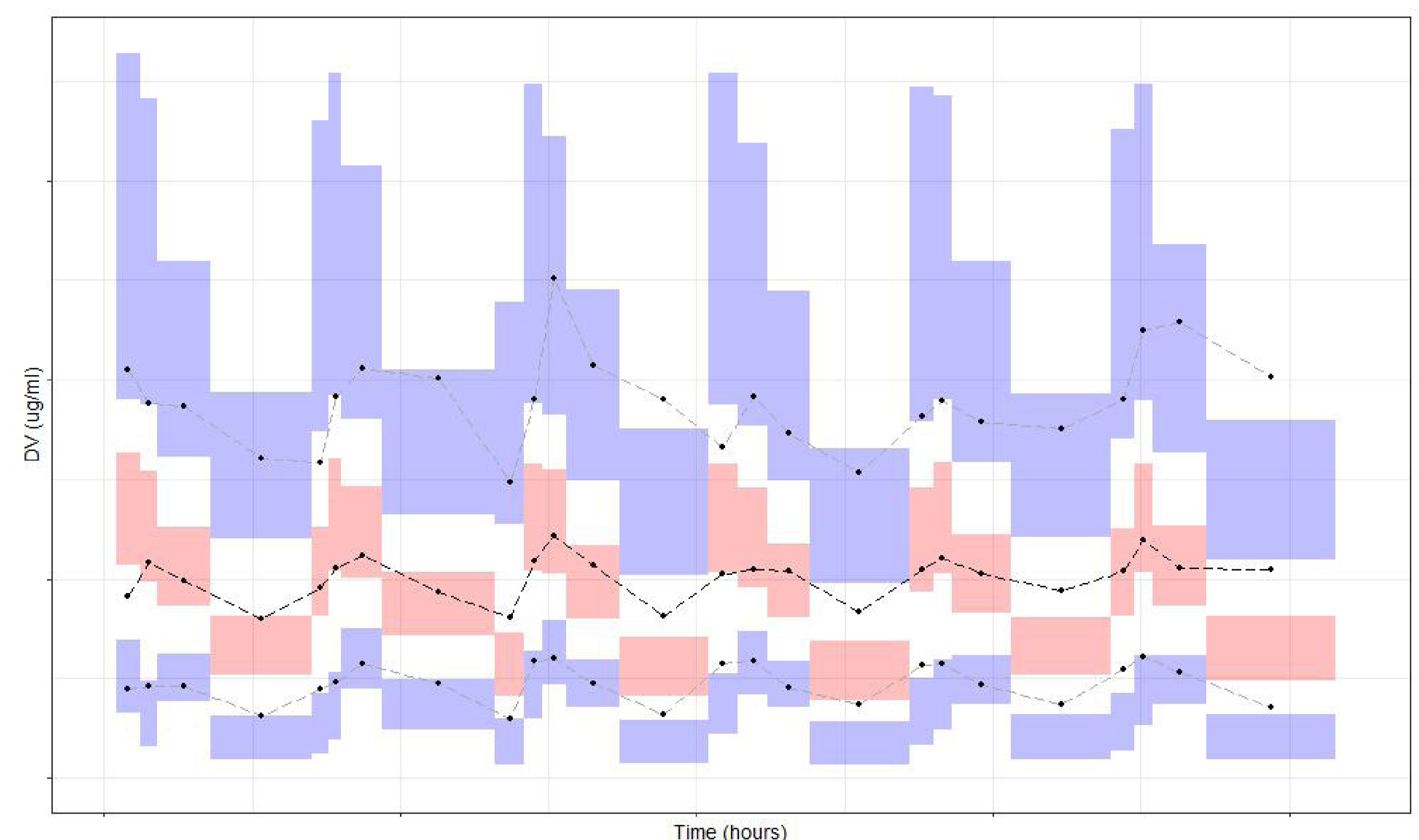
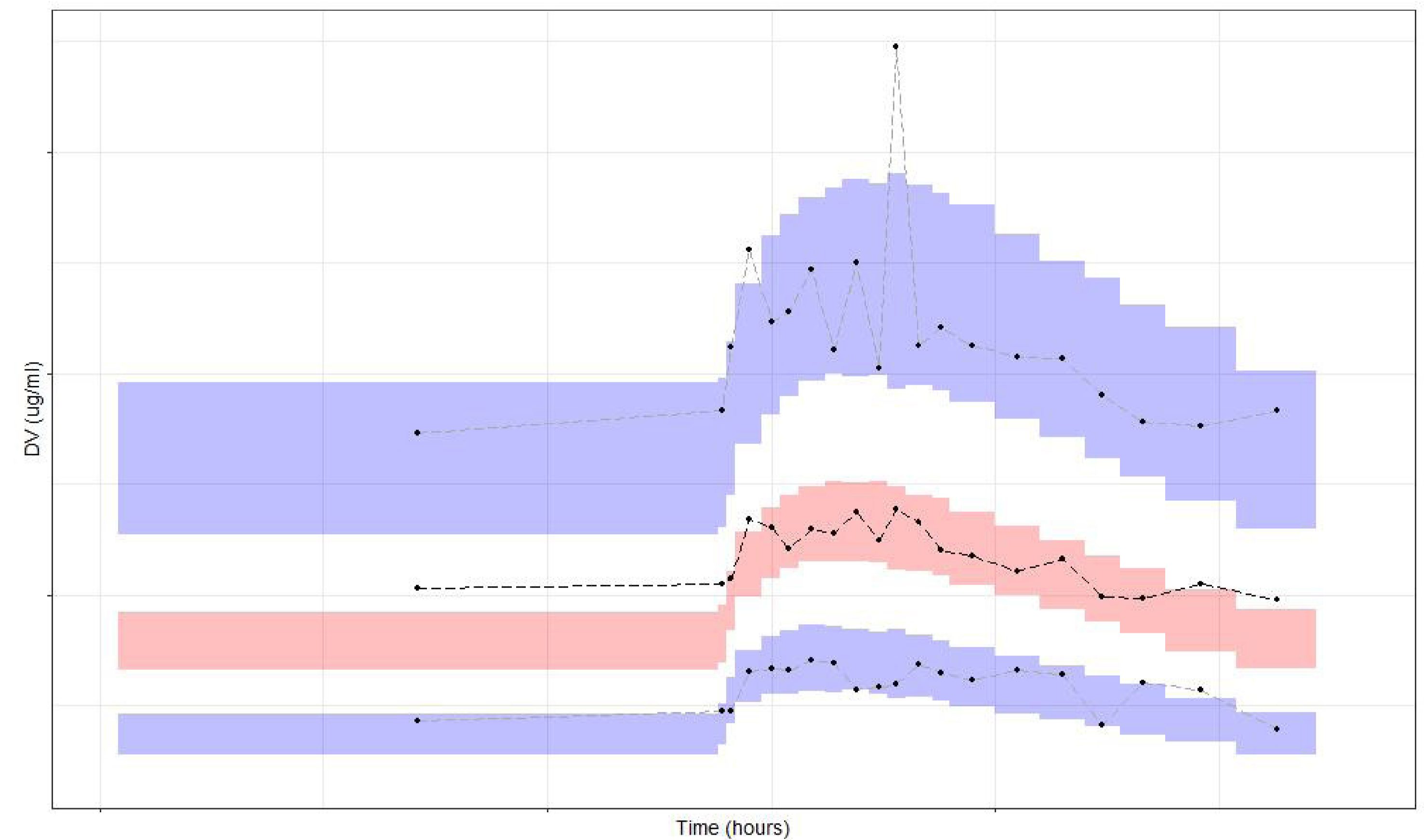
- The popPK models after single-dose administration developed so far showed that LAI PK is best described using first-order absorption, with 1- or 2-compartments, and a combined additive and proportional error model.
- The bioequivalence assessment of multiple-dose is based on steady-state PK metrics, hence the poor predictive performance at treatment onset is considered to be irrelevant.
- The importance of an adequate study design and appropriate sampling times has become more clear during this modelling exercise.

FUTURE PERSPECTIVES

Continue with model analysis and multiple-dose simulations

- This pharmacometrics exercise will be extended to the remaining LAI products and further work will focus on quantifying the sensitivity of our approach for detecting scenarios that would violate the assumptions of the single-dose to multiple-dose extrapolation.

Simulated multiple-dose predictions based on single-dose model fits seem comparable to clinical study observations

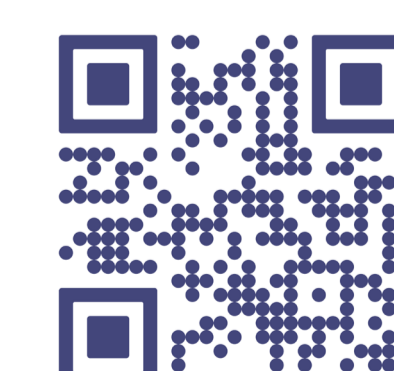


Visual predictive check (DV vs. Time) for LAI multiple-doses based on a single-dose model prediction for Product C (top figure) Product J (bottom figure) starting at presumable steady-state until the end of sampling. Black dashed line: median of the observed data, Grey dashed lines: 5th and 95th percentile of the observed data, Red bands: 95% CI of the median simulated data, Blue bands: 95% CI of the 5th and 95th percentiles in the simulated data. Green dotted lines: Approximate times of dosing for the simulated population.

“Simulating multiple-dose scenarios at a steady-state using single-dose data of LAI products seems workable”



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Let's connect!

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