

Fig. 1: Scatter plots of the observed NNZ-2566 blood concentrations in healthy subjects.

The solid line describes the median, whereas the shaded represents the 5th and 95th percentiles of the observed data. Dots depict individual measurements.

Fig. 2: Compartmental pharmacokinetic model structure.

In this diagram, K_a is the absorption rate constant, CL the total clearance, Q the intercompartmental clearance, and V_2 and V_3 represent the central and peripheral volumes of distribution, respectively.

Fig. 3: Goodness-of-fit plots.

Upper panels show the observed data (Obs) vs. individual predictions (IPred) (left) and the conditional weighted residuals (CWRES) vs. time (right). Lower panels show the observed data vs. population predictions (Pred) (left) and CWRES vs. population predictions (right).

Fig. 4: Mirror plots.

Each panel shows the goodness-of-fit plots (individual predicted vs. observed concentrations) from five randomly selected simulated data sets along with the original data (lower panel on the right).

Fig. 5: Visual predictive checks.

Observed and predicted NNZ-2566 concentration vs. time profiles in healthy subjects. In each panel, the solid and dotted lines represent the median of the simulated profiles along with the corresponding 95% confidence intervals. These results suggest absence of bias and accurate model performance, irrespective of dosing regimen.

Fig. 1S: Normalised Predictive Distribution Error (NPDE).

Top left: QQ-plot of the distribution of the NPDE vs. the theoretical $N(0,1)$ distribution. Top right: Histogram of the distribution of the NPDE along with the density of the standard Gaussian distribution. Bottom left: NPDE vs. time. Bottom right: NPDE vs. population predicted concentrations. Dashed lines in the top graphs represent the 95% prediction intervals for the normal distribution. Dashed lines in the bottom graphs represent 10th, 50th and 90th percentiles of the NPDE corresponding to the observed data. Shaded areas represent the 95% prediction intervals for the 2.5, 50 and 97.5th percentiles. Red lines/shade depict the median, whereas blue lines/shade indicate the 2.5th and 97.5th quantiles of observed data. Blue dots represent the individual observed values.