

Free IL-6 Following Treatment with Ziltivekimab in a Population with Moderate-to-Severe Chronic Kidney Disease

Bibi Toft Hellinghus¹; Jesper Falkesgaard Højen¹; Magnus Fugger¹; Christian Hollensen¹

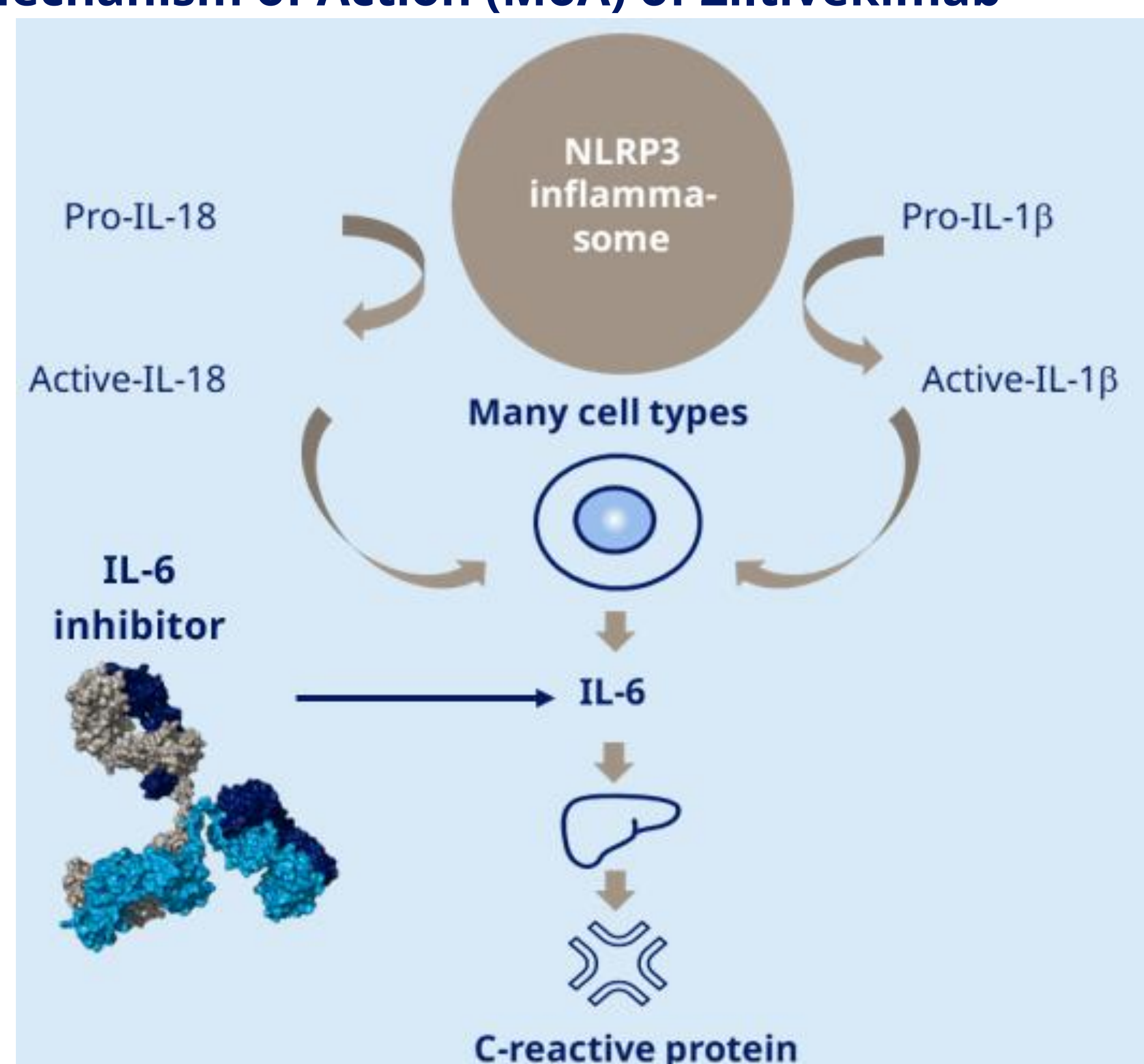
¹ Novo Nordisk A/S



Introduction & Objective

- Ziltivekimab is a human monoclonal antibody that targets interleukin 6 (IL-6), a pro-inflammatory cytokine involved in various inflammatory processes. By binding to IL-6, ziltivekimab inhibits ligand-receptor interactions, and thus downstream signaling pathways.
- Quantifying the concentration of free IL-6 is of significant scientific and clinical interest. However, it is challenging to measure free IL-6 due to the very low concentrations, typically in the order of pg/mL. The concentration of free IL-6 is crucial for understanding changes in free IL-6 levels in response to ziltivekimab treatment as well as in communication with regulatory authorities and physicians.
- To address this issue, PK/PD modelling was used to quantify the concentration of free IL-6. This model was based on available PK and total IL-6 (bound and unbound) data from samples collected at baseline and during consecutive measurements, in accordance with clinical trial protocols.

Figure 1: Mechanism of Action (MoA) of Ziltivekimab

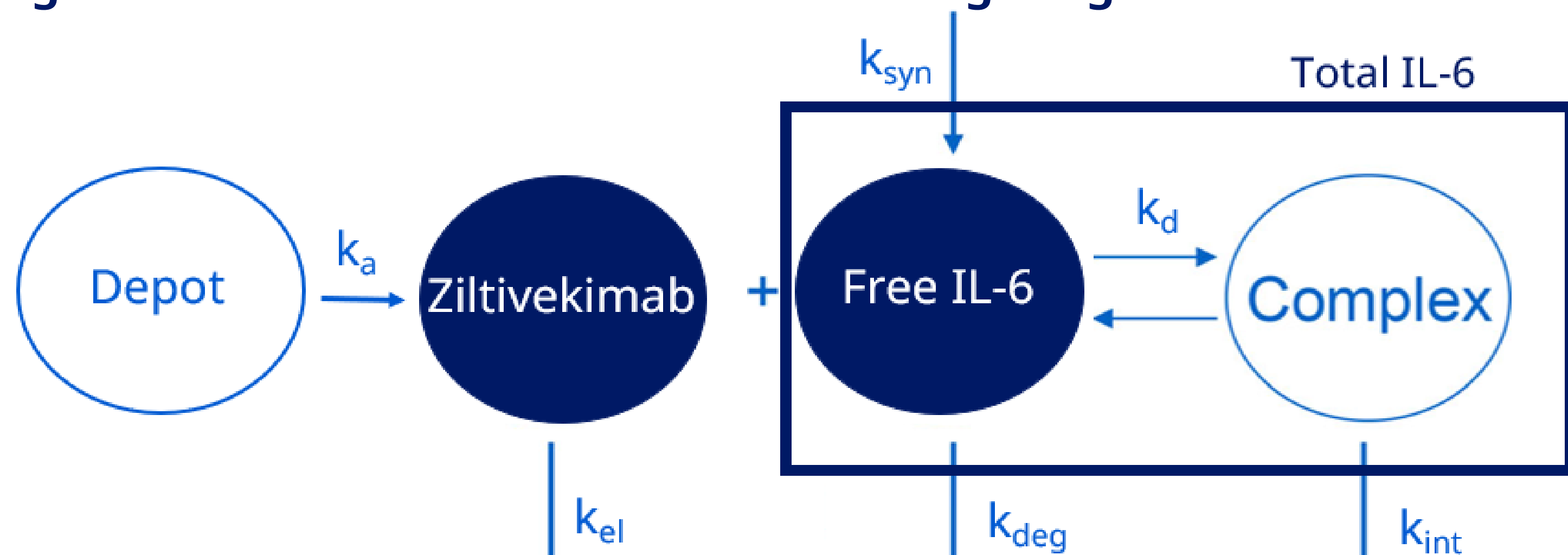


Schematic representation of the NLRP3 inflammasome activation pathway. Pro-IL-1 β and Pro-IL-18 are cleaved into their active forms, which stimulate IL-6 production across multiple cell types. IL-6 subsequently induces hepatic synthesis of C-reactive protein (CRP). This pathway is relevant for understanding the pharmacodynamic effects of ziltivekimab targeting IL-6.

Methods

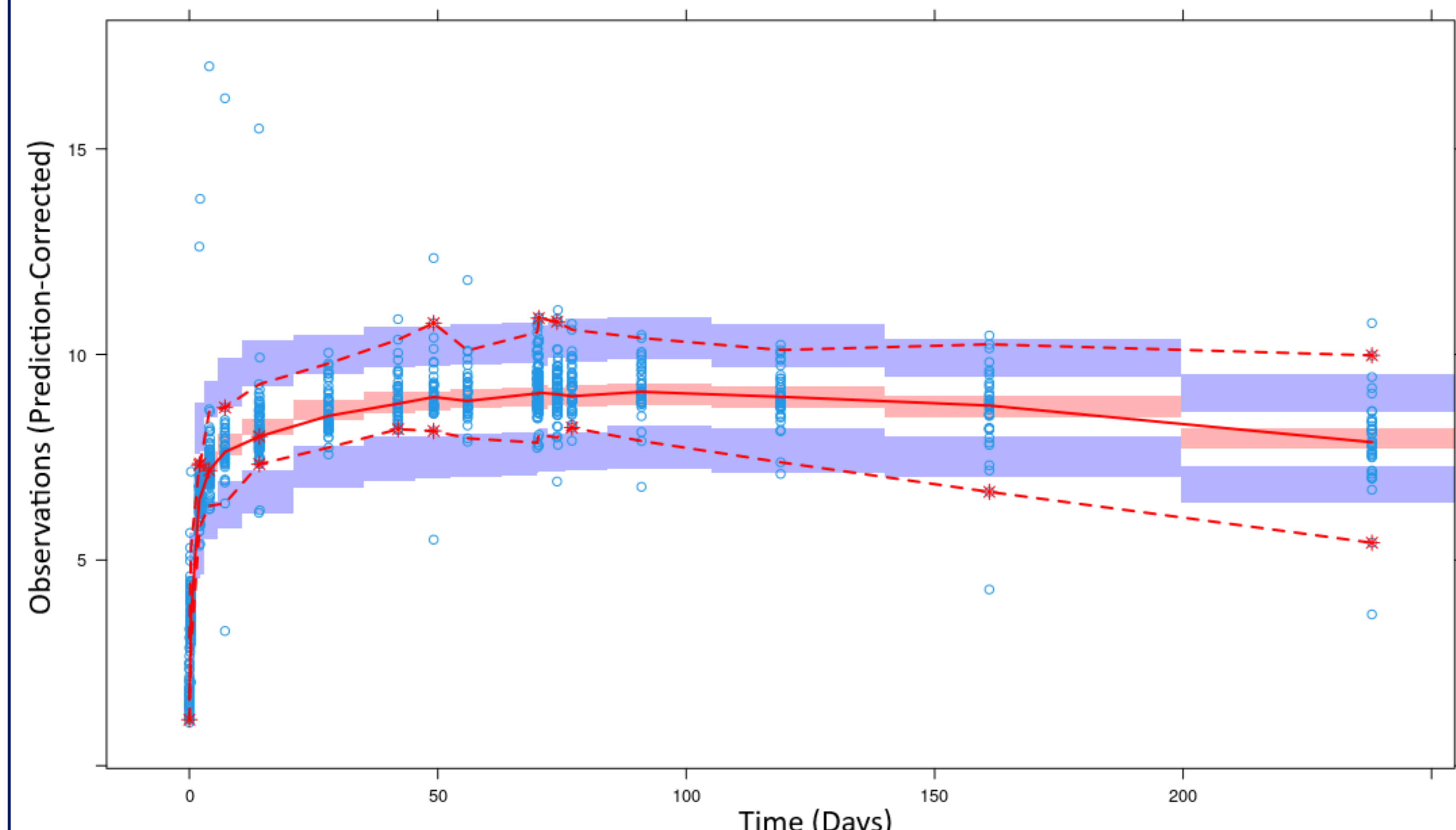
- PK and total IL-6 data were collected during clinical phase 1 and 2 trials, involving a total of 275 subjects with moderate to severe chronic kidney disease.
- The subjects were administered ziltivekimab at varying doses: 2, 6, or 20 mg intravenously (IV) or 7.5, 15, or 30 mg subcutaneously (SC).
- The PK/PD analysis was performed using a non-linear mixed effect modelling approach in NONMEM. Both the PK and PK/PD part covariates were evaluated using a forward selection method with a p-value threshold of 0.05, followed by a backward inclusion method with a p-value threshold of 0.001.
- The PK/PD analysis was evaluated using the -2 log-likelihood objective function value, goodness-of-fit plots, and visual prediction checks.
- Data management, visualization of data, and model predictions were performed using R and Rstudio.

Figure 2: TMDD Model for Ziltivekimab Targeting IL-6



Target-mediated drug disposition (TMDD) model for ziltivekimab targeting IL-6 consisting of following components: Complex: concentration of the IL-6 complex; free IL-6: concentration of free IL-6; k_a : absorption rate constant; k_d : dissociation constant; k_{deg} : degradation rate constant; k_{el} : elimination rate constant; k_{int} : internalization rate constant; k_{syn} : synthesis rate constant.

Figure 3: Prediction-Corrected Visual Predictive Check (pcVPC) of Total IL-6 Based on Data from a Multiple Ascending Dose Trial with Ziltivekimab (2, 6, and 20 mg IV Q2W) in Haemodialysis Patients

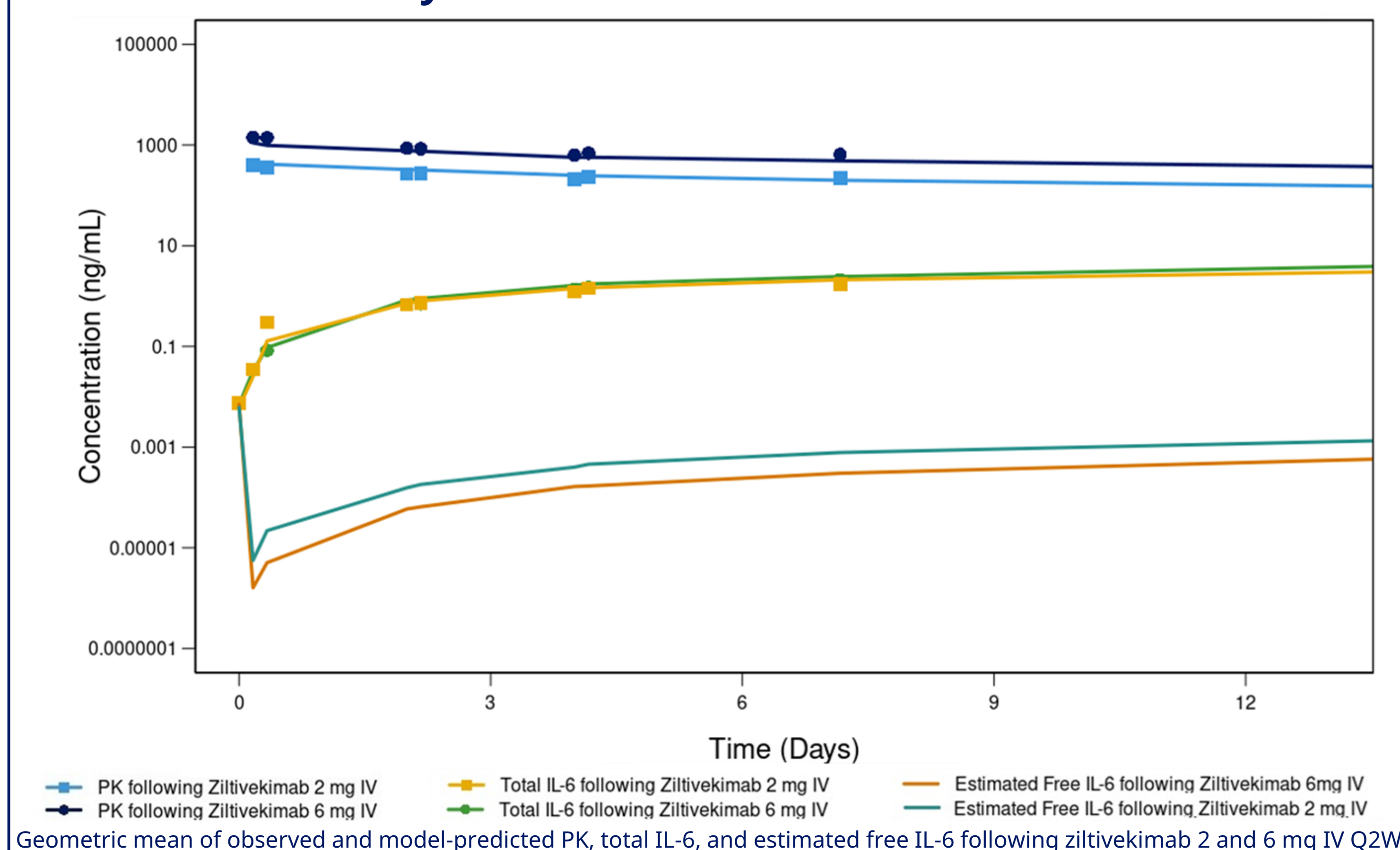


Blue circles represent observed data; red solid line shows the median of the observed data; red dashed lines indicate the 5th and 95th percentiles of the observed data; the shaded red area represents the 95% confidence interval (CI) around the simulated median; blue shaded areas represent the 95% CI around the simulated 5th and 95th percentiles.

Results

- The PK/PD model was developed sequentially, first to the PK of ziltivekimab and subsequently to the total IL-6 data.
- Initially, a two-compartment PK model with first order absorption and elimination was applied to the PK data of ziltivekimab.
- Using the post hoc estimates from the PK model, total IL-6 concentrations were described by an TMDD-Qss model, which incorporated a baseline concentration of IL-6, a degradation rate constant (k_{deg}) of IL-6, and a dissociation constant (k_d) for the binding of ziltivekimab to IL-6. Measured estimated glomerular filtration rates (eGFR) were exponentially integrated into the model on k_{deg} . Furthermore, inter-individual variability was exponentially added to all PD parameters.
- The concentration of free IL-6 was determined by subtracting the ziltivekimab/IL-6 complex from the total IL-6.
- The model demonstrated a dose-dependent reduction in free IL-6, supporting the expected mechanism of action of ziltivekimab.

Figure 4: Model Evaluation of PK, Total and Free IL-6, During the First 2 Weeks Post-Dose Following Ziltivekimab 2 and 6 mg IV in Haemodialysis Patients



Geometric mean of observed and model-predicted PK, total IL-6, and estimated free IL-6 following ziltivekimab 2 and 6 mg IV Q2W.

Conclusion

- The developed TMDD model is the first to characterize the relationship between the plasma concentration of ziltivekimab and free IL-6.
- This innovative TMDD model provides valuable insights and enhances the understanding of ziltivekimab's mechanism of action, which may help to explain clinical outcomes and optimize therapeutic strategies.
- The reduction in free IL-6 supports the expected mechanism of action of ziltivekimab.