



Optimizing IMC-001 Dosage Regimens Using Target Mediated Drug Disposition Model : Enhancing Therapeutic Efficacy and Safety in Cancer Treatment

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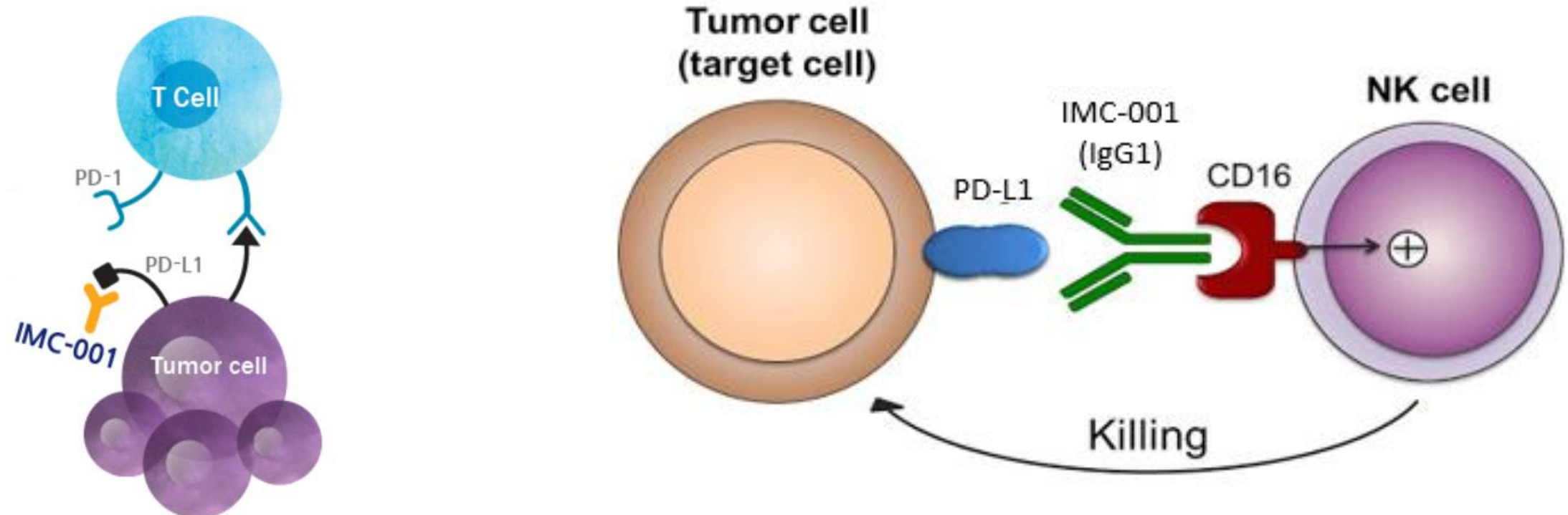
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BACKGROUND

- The emergence of anti-programmed cell death ligand 1 (PD-L1) inhibitors marks a significant advancement in cancer therapeutics, specifically targeting the mechanisms of immune evasion within tumors. These inhibitors, by blocking PD-L1 interactions, enhance the body's immune response against cancer cells, thereby improving therapeutic outcomes.
- IMC-001 is a fully human PD-L1 recombinant monoclonal antibody designed to bind strongly to PD-L1, preventing its interaction with programmed cell death protein 1 (PD-1) and B7-1 (CD80) which increases the anti-cancer activity of T-cell. Preclinical studies have demonstrated that IMC-001 exhibits robust dose-dependent efficacy, with no evidence of toxicity at doses ranging from 1 mg/kg to 10 mg/kg in animal models, including cynomolgus monkeys.



Mode of action of IMC-001

- In a Phase 1 clinical trial, which involved a dose escalation study ranging from 2 mg/kg to 20 mg/kg, IMC-001 showed no dose-limiting toxicity (DLT). This indicates a favorable safety profile and supports further investigation into its optimal dosing regimen. The trial results provide a promising outlook for the use of IMC-001 in cancer treatment.

OBJECTIVES

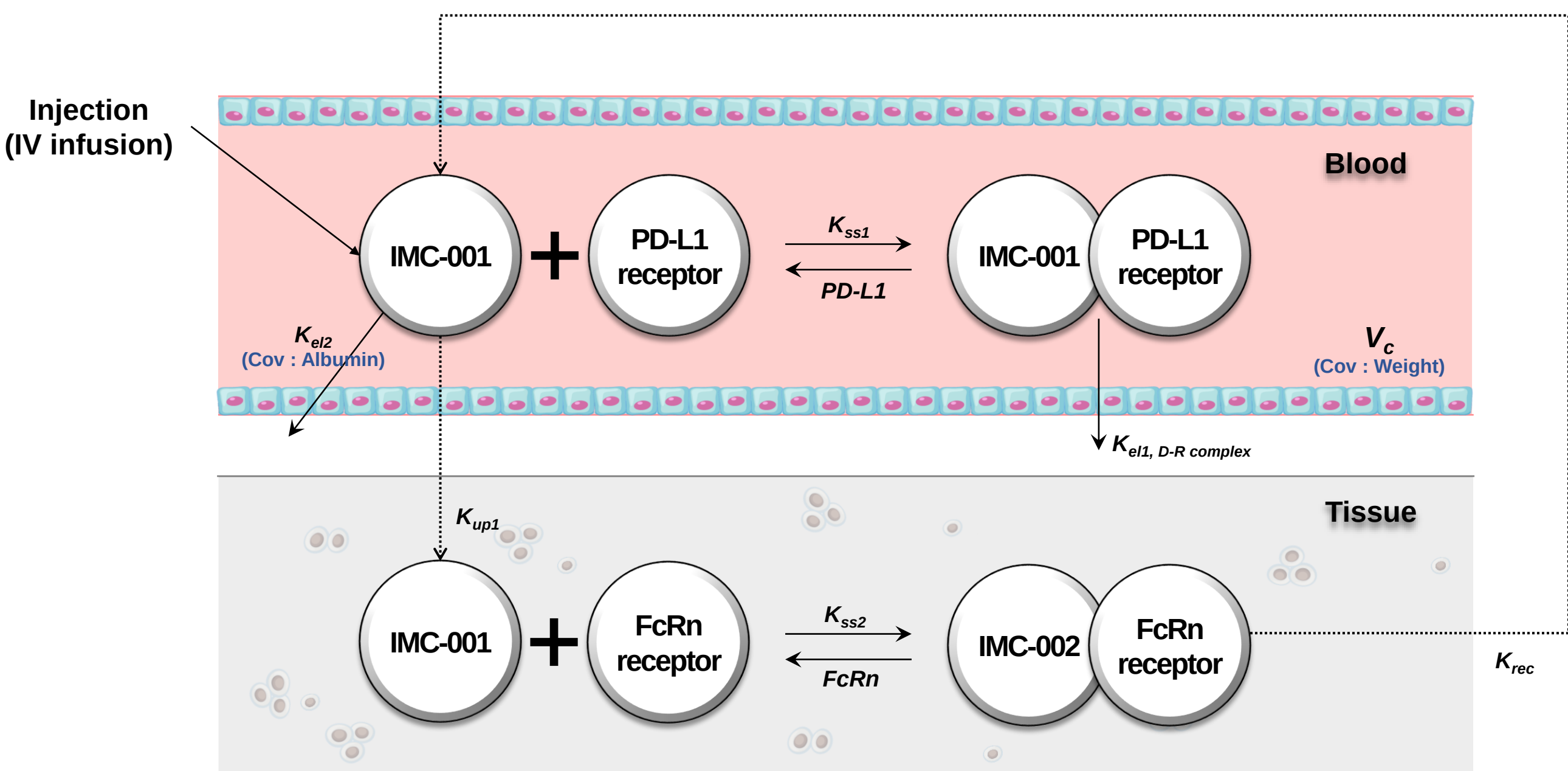
- This study aims the optimization of IMC-001 dosage regimen through Target-Mediated Drug Disposition (TMDD) modeling**
 - Enhancing therapeutic efficacy and minimizing the adverse effects in caner patients through TMDD modeling
 - Determination of effective and safe dosage regimen through population pharmacokinetic modeling

METHODS

- Dataset**
 - To optimize the dosage regimen for IMC-001, data from Phase 1 and Phase 2 clinical trials were utilized.
 - Phase 1 involved a dose escalation study with doses of 2, 5, 10, 15, and 20 mg/kg, administered to 3 patients per group. Phase 2 focused exclusively on the 20 mg/kg dosage level with a cohort of 20 patients. Both phases included multiple-dose, 1-hour intravenous (IV) infusions.
- Pharmacokinetic Modeling**
 - Target-Mediated Drug Disposition (TMDD) modeling was employed to analyze the pharmacokinetic (PK) profile of IMC-001. This model incorporated FcRn recycling and utilized the quasi-steady-state (QSS) approximation to simplify the equations. The TMDD model is particularly suitable for monoclonal antibodies, which often exhibit non-linear pharmacokinetics due to target binding.
 - Incorporating the FcRn recycling mechanism into TMDD modeling allows for a consideration of the pharmacokinetic characteristics of IgG-based therapeutics.
 - As the method used for estimating the parameters of the model, first-order conditional estimation with interaction (FOCEI) is designated as the default.
 - Some of parameters are fixed as the biologically based value.
- Covariate Analysis**
 - Covariate searching was conducted to identify factors that significantly impact the pharmacokinetics of IMC-001. This step ensures that the model accounts for patient-specific variables that could influence drug distribution, metabolism, and elimination, thus providing a more accurate and individualized dosage regimen.
- PK Simulations**
 - PK simulations were performed to compare key PK parameters (AUC_{τ} , C_{max} , and C_{trough}) across various dosage regimens: Q2W (every two weeks), Q4W (every four weeks), Q6W (every six weeks), and Q8W (every eight weeks). These simulations involved multiple dosing, with administration of 6 cycles to achieve a steady state. The aim was to determine the optimal dosing schedule that balances efficacy and safety.
- Software and Tools**
 - The simulations and modeling were conducted using NONMEM 7.5, a widely used software for population pharmacokinetic and pharmacodynamic modeling. This tool allows for complex model building and simulation, enabling a thorough analysis of the dosing regimen for IMC-001.
 - Data manipulation and plotting were conducted using the programming language of R. For data manipulation, the open-source libraries ‘dplyr’, ‘tidyr’ were used. Graphical plotting was conducted using ‘ggplot2’, the open-source library.

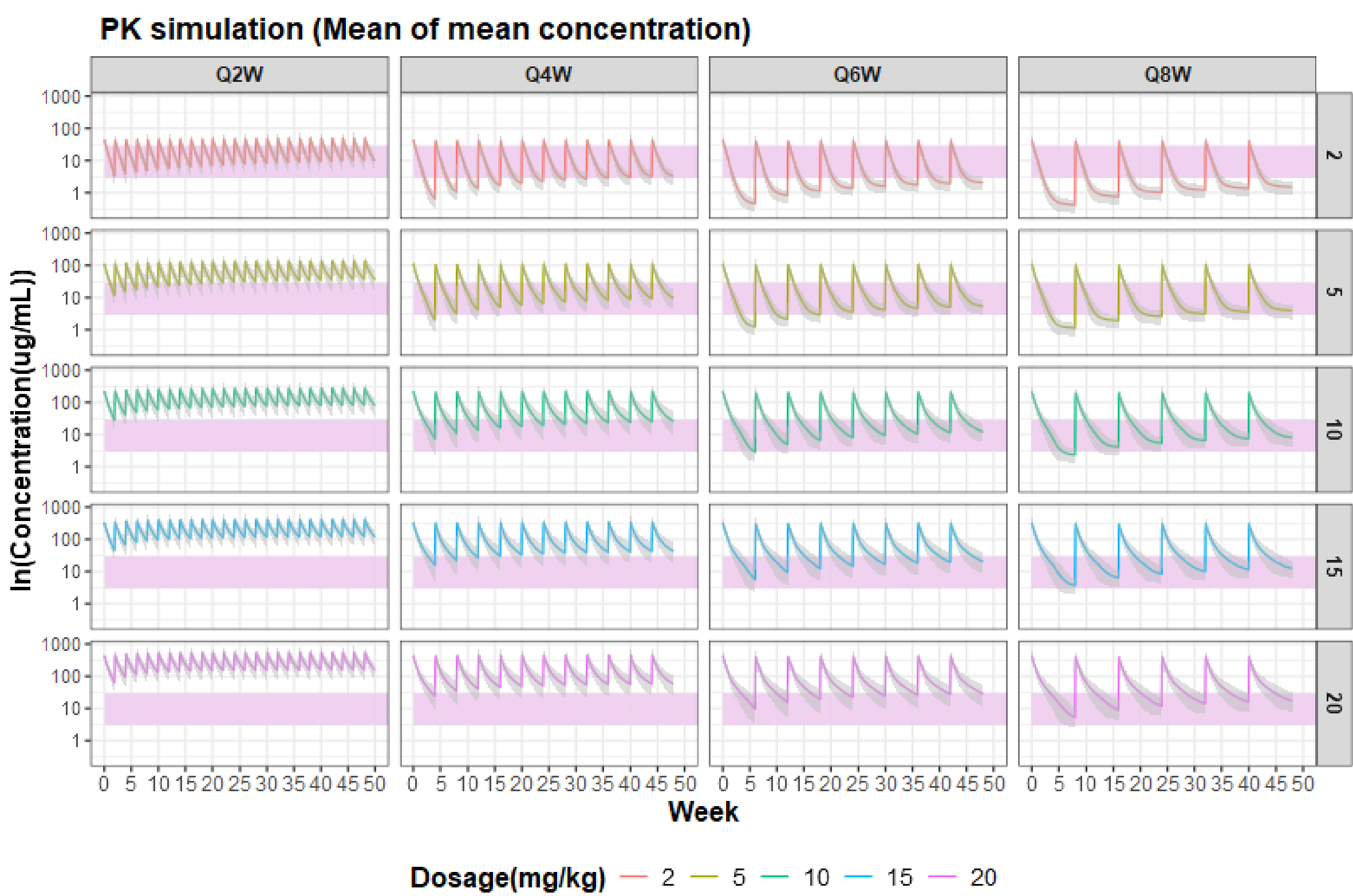
RESULTS

- Model Development**
 - Framework: The final pharmacokinetic model incorporated the FcRn recycling compartment within the Target-Mediated Drug Disposition (TMDD) framework



Final model scheme

- Covariate search: Covariate selection was performed using the Stepwise Covariate Model (SCM) approach. This method identified two significant covariates: **patient body weight**, which influences the central volume of distribution, and **albumin** level, which affects the elimination of free IMC-001. These covariates were incorporated to account for individual variability in drug distribution and elimination.
- Fixed parameters: To integrate physiological factors, four parameters were fixed: the **dissociation constant between PD-L1 and IMC-001** at 0.00155 $\mu\text{mol/L}$, the **dissociation constant between FcRn and IMC-001** at 71.3 $\mu\text{mol/L}$, the **total concentration of FcRn** at 0.291 $\mu\text{mol/L}$, and the **degradation rate for the IMC-001 and PD-L1 complex** at 0.225 1/h. The estimated parameters were consistent with *in vitro* data and references.
- PK simulation and parameter comparison**
 - Comparison criteria: AUC_{τ} , C_{max} , and C_{trough} .
 - The primary objective: Finding dosing intervals that provide comparable systemic exposure to the 20 mg/kg Q2W regimen, which was effective in the Phase 2 trial.
 - Simulation regimen: Q2W, Q4W, Q6W, and Q8W IV 20 mg/kg regimens
 - Pink area: *in vivo/in vitro* therapeutic concentration of IMC-001

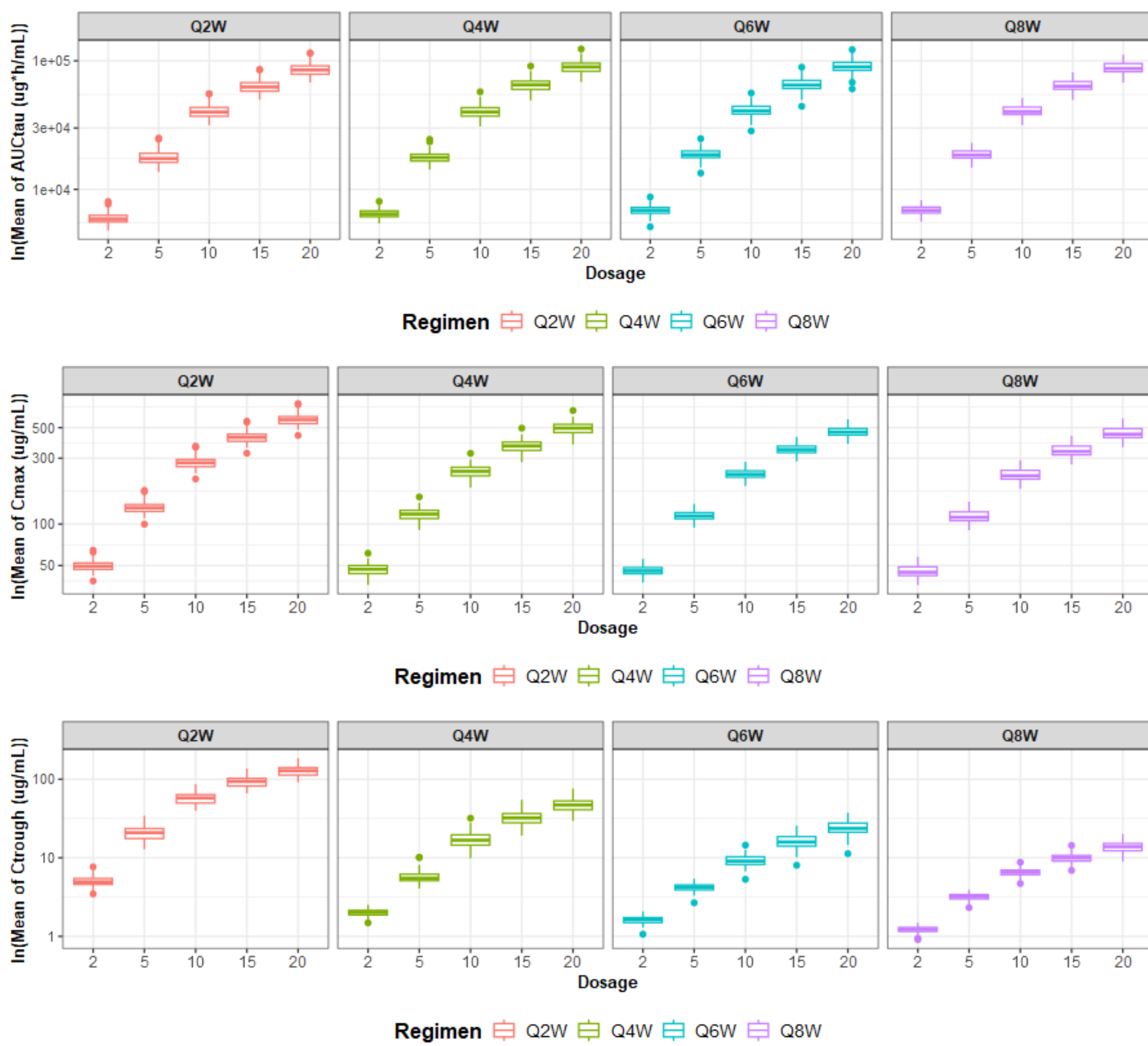


PK simulation result plot – Time vs Concentration

- PK parameter mean value comparison

PK parameter	Unit	Q2W	Q4W	Q6W	Q8W
AUC_{τ}	$\mu\text{g} \cdot \text{h/mL}$	81598.5	82426.2	85476.7	86093.8
C_{max}	$\mu\text{g/mL}$	582.3	491.2	470.2	465.9
C_{trough}	$\mu\text{g/mL}$	130.8	46.9	25.3	15.9

PK parameter table – AUC_{τ} , C_{max} , C_{trough}



PK simulation result plot – AUC_{τ} , C_{max} , C_{trough}

- Result interpretation: The simulations demonstrated that alternative regimens (Q4W, Q6W, Q8W) yielded **similar AUC_{τ} values** compared to the Q2W 20 mg/kg regimen, indicating comparable overall exposure. However, the alternative regimens resulted in **lower peak levels (C_{max})** of IMC-001, which could potentially **reduce pharmacokinetic-related safety concerns**. Although the trough levels (C_{trough}) were lower for the alternative regimens, the systemic exposure (AUC_{τ}) was maintained, suggesting that therapeutic efficacy could still be achieved.

CONCLUSION & DISCUSSION

- Based on the simulations, the 20 mg/kg Q2W regimen for IMC-001 could potentially be replaced by Q4W, Q6W, and Q8W regimens. These alternative regimens maintain comparable systemic exposure while reducing peak levels, potentially minimizing pharmacokinetic-related safety issues.
- The use of TMDD modeling incorporating FcRn recycling for IMC-001 has proven instrumental in optimizing dosage regimens. This finding supports the feasibility of less frequent dosing intervals for IMC-001, offering flexibility in clinical application without compromising efficacy

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