A mechanistic target-mediated drug disposition model to select an optimal biweekly dosing regimen for GC1118, a novel monoclonal antibody against the epidermal growth factor receptor

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**Objectives:** To develop a mechanistic population pharmacokinetic (PK) model of GC1118, a novel monoclonal antibody inhibiting the epithelial growth factor receptor (EGFR), using concentration-time data obtained from the clinical trial with GC1118 after repeated once-weekly intravenous administration and to select an optimal biweekly dosing regimen based on the model for further clinical development.

**Methods:** GC1118 was intravenously infused over 2 hours once weekly for four consecutive weeks at 0.3-5.0 mg/kg. Serial blood samples for PK analysis were collected up to 504 hours after the last dose of GC1118. A mechanistic target mediated drug disposition (TMDD) model was developed using NONMEM (version 7.3, ICON Development Solutions, Hanover, MD, USA), and qualified by visual predictive checks. The final population PK model was used to simulate concentration-time data for various biweekly dosing regimens to choose from one for further development in the second part of the FIH study with GC1118.

**Results:** A total of 22 patients with advanced solid tumors completed the PK study. A mechanistic TMDD model adequately described the observed concentration-time data of GC1118. Based on a series of simulation experiments using the final PK model, a loading dose of 12.0 mg/kg followed by a biweekly maintenance dose of 8.0 mg/kg was expected to yield a trough concentration comparable to that seen after once weekly administration at 4.0 mg/kg, a recommended phase 2 dose. Furthermore, the maximum concentration after this biweekly dosing regimen was anticipated not to exceed that noted in patients experiencing dose limiting toxicities after receiving 5.0 mg/kg once-weekly regimen.

**Conclusions:** A mechanistic TMDD model of GC1118 was adequately developed and used successfully to select an optimal biweekly dosing regimen for further development.