Evaluation of subcutaneous bioavailability of CNTO 3157 in healthy volunteers using a two-compartment population PK model with additional non-linear clearance function

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Objective: CNTO 3157 is a human monoclonal antibody directed to antagonize toll like receptor-3 (TLR3) and is developed for the treatment of TLR3 mediated inflammatory immune diseases. CNTO 3157 demonstrated non-linear pharmacokinetics (PK) in the FIH clinical study following intravenous (IV) administration. The subcutaneous (SC) bioavailability of CNTO 3157, if evaluated using the conventional method, would result in dose-dependent values. The study is to evaluate the true SC bioavailability in a Phase 1 clinical trial.

Methods: Two Phase 1 clinical pharmacokinetic studies of CNTO 3157 were conducted. CNTO3157ASH1001: a 2-part FIH study of single ascending doses of CNTO 3157 in healthy subjects (0.003 to 10 mg/kg single dose IV) and of multiple doses in stable asthmatic subjects (4 weekly doses of 3 or 10 mg/kg IV). CNTO3157NAP1001: a safety and PK study of fixed dose SC administration at 100, 300 and 600 mg, and 300 mg IV. A 2-compartment population PK model with first-order elimination, an additional Michaelis Menten elimination function, and a first order SC absorption function was used to analyze the data and to estimate bioavailability. The data was also analyzed using conventional non-compartment PK analysis.

Results: The model described non-linear PK of CNTO 3157 very well as assessed by goodness of fit. By assuming first order absorption kinetics following SC administration, the model estimated the bioavailability of CNTO 3157 to be 79% and the results also determined no dose dependency. Utilizing a conventional non-compartment absolute bioavailability approach, the calculated bioavailability ranged from 29% to 88% dependent on SC dose level and therefore on the dose level selected for the IV cohort as well.

Conclusion: The 2-compartment population PK model with additional non-linear clearance function successfully described the data. The absorption of CNTO 3157 following SC administration demonstrated first order kinetics. Although CNTO 3157 exhibited non-linear PK, the SC bioavailability was not dose-dependent in the dose range tested.