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Population Pharmacokinetics of Siplizumab (MEDI-507): Implications for Dosing

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Poster: Applications- Biologicals/vaccines

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Objectives: Siplizumab (MEDI-507), a humanized IgG1k class monoclonal antibody which targets CD2 expressing T- and NK-cells, is being evaluated in an ongoing open label Phase I dose-escalation trial in patients with CD2-positive lymphoproliferative diseases. The aim of this report is to describe a population pharmacokinetic model of siplizumab and simulations of alternative doses/regimens performed for optimization of dosing.

Methods: 490 serum siplizumab samples were collected from 25 patients who received 0.4-4.8 mg/kg of siplizumab as 1- 3 consecutive daily doses every 14 days for 1-8 cycles. The population pharmacokinetic analysis was performed using NONMEM. Linear and nonlinear one and two compartment models were evaluated. Simulations were performed to identify doses and dosing regimens that would maintain drug concentrations above target levels necessary for saturation of CD2 receptors.

Results: Siplizumab pharmacokinetics was described by one-compartment model with 2 parallel mechanisms of clearance, linear and Michaelis-Menton (MM) elimination. The half-life of the linear portion of elimination (presumably, FcRn mediated) was 31 days, consistent with expectations, while MM elimination (target-mediated clearance) had a short half-life (38 hours at concentrations below Km of 15 µg/mL**)** suggesting suboptimal target saturation. Pharmacokinetics did not change over time, which was expected, since no immunogenicity was observed. Simulations of various dosing regimens suggested that doses > 4.8 mg/kg weekly are necessary to maintain drug concentrations above target level (2xKm, 30 µg/mL, the level at which half-life of target-mediated clearance increases 3 times) for 90% of patients.

Conclusions: Siplizumab concentrations follow one-compartment kinetics with linear FcRn-mediated and nonlinear target-mediated clearance. The short half-life of target-mediated clearance suggests that tissue target saturation is suboptimal at doses/regimens studied thus far. Dose escalation was accelerated based on simulations, with weekly doses $\geq$ 4.8 mg/kg, to maintain concentrations above the target level and to possibly increase target saturation in the tissues.