Population Pharmacokinetics of an anti-repulsive guidance molecule A (RGMa) antibody for treatment of multiple sclerosis, is well characterized by a 3 compartment model utilizing target mediated drug disposition

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Objectives: Characterize the population pharmacokinetics of a novel mechanism of action (anti-RGMa) monoclonal antibody in a healthy volunteer first-in-human study

Methods: The population pharmacokinetics anti-RGMa antibody was evaluated in a double-blind, placebo-controlled, single ascending dose, first-in-human study in healthy volunteers. Subjects (N=40) were divided into 5 groups to receive single IV doses an anti-RGMa antibody or placebo (randomized 6:2) ranging from 50-1600 mg. Serial blood serum samples were collected from subjects up to 272 days post-dose for PK assessment. Concentrations from all subjects exposed to the anti-RGMa antibody were used for nonlinear mixed effects analyses. Two and three-compartment models were explored incorporating target mediated drug-disposition using the Michaelis-Menten approximation. Covariates effects on central compartment volume of distribution (V) and clearance (CL) were assessed. The relative importance of covariates was examined by the likelihood ratio test. Inter-individual variability was characterized using exponential error models and residual variability using a mixed error model. Population analyses were performed using NONMEM®, Version 7.3 with the first-order conditional estimation method with interaction used to estimate population PK parameters.

Results: The population PK model was built using 634 concentration measurements from 30 subjects. Optimal characterization of the serum concentration data was achieved using a three-compartment model with TMDD incorporated on the central compartment elimination using the Michaelis-Menten approximation (Figure 1). Standard error for the parameter estimates ranged from 2.2-25%. The final covariate selection process identified one covariate, weight on V, as a statistically significant covariate (p<0.001).

Conclusions: A population pharmacokinetic model was developed to characterize a novel anti-RGMa antibody following a single dose in healthy volunteers. PK nonlinearity was well described by a 3 compartment model incorporating TMDD. Weight was the only statistically significant covariate on central clearance.

Figure 1. Final population PK model structure.