Latent Variable Approach to Assess the Time-Varying Effect of Immunogenicity on the Pharmacokinetics of Elotuzumab in Patients with Multiple Myeloma

C. Passey¹*, L. Gibiansky², A. Roy¹, A. Bello¹, M. Gupta¹

¹Bristol-Myers Squibb, ²QuantPharm LLC

Background: Elotuzumab (ELO) is a humanized anti-SLAM7 IgG1 monoclonal antibody, under development for multiple myeloma. A model based analysis was conducted to evaluate the impact of immunogenicity on the PK of ELO.

Methods: ELO PK was characterized by a two compartment model with parallel linear and Michaelis-Menten elimination from the central compartment, and additional target-mediated elimination from the peripheral compartment. Population Pharmacokinetic (PPK) model was developed using the Monte Carlo EM method with importance sampling in NONMEM. The final PPK model was then used to evaluate an ad-hoc effect of immunogenicity on the linear clearance (CL) of ELO. Specifically, a latent variable \( \rho \) was introduced, equal to zero at time zero and at time points where ADAs were not detected and equal to one at time points where ADAs were detected. At time points between ADA measurements, a sigmoid function with estimated onset and offset times was used to interpolate \( \rho \) as a function of time.

Results: Population PK analysis indicated that CL and \( V_C \) were independent of ADA status; however, target-mediated elimination was increased (\( V_{MAX} \) was higher and \( K_M \) was lower) in ADA-positive patients; \( V_{MAX} \) increased with increasing baseline M-protein. In majority of ADA positive patients, ADAs occurred early on in treatment, was transient and resulted in corresponding transient increases in CL. CL appeared to return to baseline values at later timepoints when ADAs were no longer detected. The increase in ELO CL due to immunogenicity at times when ADA were detected was 110% (95% CI: 55.8% - 218%), and variability of this increase was very large (CV = 215%). However, model-based simulations indicated lower ELO exposures in ADA-positive patients than in ADA-negative subjects, which may not be due to a direct causal relationship, but could be associated with higher baseline serum M-protein in ADA-positive patients.

Conclusion: The relationship between ELO immunogenicity and PK appears to be confounded by the influence of baseline M-protein concentration.