Model-Based Analysis to Support Clinical Pharmacology Profiling of Elotuzumab in Patients with Multiple Myeloma

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Background: Elotuzumab (ELO) is a humanized anti-SLAM7 IgG1 monoclonal antibody under development for combination use with lenalidomide/dexamethasone (Len/Dex), and bortezomib/dexamethasone (Bor/Dex) for the treatment of relapsed or refractory multiple myeloma (MM). A model based analysis was conducted to support the clinical pharmacology profiling of ELO by characterizing ELO’s PK and determining effect of covariates on PK and exposure parameters in MM patients.

Methods: The PK of ELO was described by a population pharmacokinetics (PPK) model, developed using 6958 serum concentration values from 375 MM patients receiving ELO at doses of 10 or 20 mg/kg in 4 clinical studies. The PPK model was estimated by nonlinear regression using the NONMEM software program and the Monte Carlo expectation-maximization (EM) method with importance sampling (IMPMAP). The impact of the following baseline covariates on PK was assessed: body weight, age, race, sex, renal function (as measured by eGFR), hepatic function, ECOG performance status, LDH, albumin, Len/Dex co-administration, serum M-Protein, and β2-microglobulin. The final PPK model was developed by retaining covariates that improved the Bayesian Information Criterion (BIC). The final model was then evaluated and refined using data from another study of ELO in combination with Bor/Dex.

Results: ELO PK is characterized by a two compartment model with zero order IV infusion, parallel non-specific (linear) and Michaelis-Menten elimination from the central compartment, and additional target-mediated elimination from the peripheral compartment. Non-specific clearance of ELO (CL) increases with increasing body weight; body-weight based dosing of ELO results in uniform ELO exposures across body weight ranges. Co-administration of Len/Dex or Bor/Dex background therapy resulted in a decrease of ELO non-specific clearance by 35% and 50%, respectively, relative to ELO monotherapy. Target-mediated elimination of ELO increases with increasing baseline serum M-protein, resulting in lower exposure in patients with high baseline serum M-protein concentrations. None of the other tested covariates had clinically relevant (<20%) effects on elotuzumab CL.

Conclusion: This analysis indicated that ELO PK was non-linear.