Population Pharmacokinetics and Exposure-Response Relationships of Belimumab Following Subcutaneous Administration in Subjects with Systemic Lupus Erythematosus

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Objectives: To characterize the population pharmacokinetics (popPK) and exposure-response of belimumab following subcutaneous (SC) administration in patients with SLE.

Methods: Serially sampled Phase I PK data in healthy volunteers (n=134, BEL114448/NCT01583530, BEL116119/NCT01516450) and Phase 3 PK (n=554, BEL112341/NCT01484496) and clinical response data in systemic lupus erythematosus (SLE) patients were analyzed with a non-linear mixed effects modeling approach using NONMEM. Following popPK model development, a logistic regression model for efficacy response (SRI; SLE Responder Index) was developed using a hybrid full model/back ward eliminate approach.

Results: The PK of belimumab administered SC was best described by a linear 2-compartment model with first order absorption and absorption lag time. The bioavailability of belimumab was estimated to be 74%. The population estimates for CL, Vss and terminal half-life were 204 mL/day, 4950 mL, and 18.3 days, respectively. In addition to allometric body weight scaling of CL, Q, Vc, Vp, significant covariate effects (α=0.001) in the final model included BMI on Vc, and the neonatal Fc-receptor related effects of albumin and IgG on CL (Fig.1). Simulations with PK parameters from this and the intravenous (IV) [1] popPK analysis, demonstrated that weekly 200 mg SC dosing results in steady-state Cavg equivalent to 10 mg/kg IV Q4Wk regimen. In the final SRI logistic regression model Cavg was not significant (α=0.05); only baseline disease activity, proteinuria and race were significant predictors of response.

Figure 1: Covariate Effect of Baseline Albumin (A) and IgG (B) on CL.

Conclusions: The final SC popPK model parameters were consistent with results for the belimumab IV popPK analysis [1] and other IgG1 mAbs without substantial target-mediated disposition. These PK and PK/PD results indicate that 200 mg qw belimumab dosing is appropriate for subcutaneous administration to SLE patients and that no dose adjustments based on subject characteristics are required.

Reference: