Population Pharmacokinetics and Pharmacodynamics of the Effect of Sarilumab on DAS28-CRP in Patients With Rheumatoid Arthritis

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Objectives: Sarilumab is a human mAb blocking the IL-6Ra in development for rheumatoid arthritis (RA). Study objectives were to develop and qualify a population pharmacokinetic and pharmacodynamic (PopPK/PD) model describing the time course of DAS28-CRP in RA patients with inadequate response to DMARDs or TNF-ɑ antagonists and to identify covariates influencing PK/PD relationships using pooled phase 2/3 data.

Methods: A sequential approach was used: a PopPK model was developed first, followed by PopPK/PD model development. Model-predicted individual concentration time course was used to develop a PopPK/PD model for DAS28-CRP over time after subcutaneous administrations of sarilumab 100 to 200 mg every week (qw) or every 2 weeks (q2w) (N=2082). Full model with backward elimination was used to identify the final covariate model. The final PopPK/PD model was evaluated by visual predictive check and bootstrap.

Results: DAS28-CRP time course was described by an indirect-response model linking sarilumab concentrations with DAS28-CRP via inhibition of DAS28-CRP input rate. Population parameter estimates in the final model translated into a population mean decrease of DAS28-CRP from baseline of 6.06 to 2.67, with IC₅₀ of 2.32 mg/L. Effect on DAS28-CRP reduction from baseline was less for 150 vs 200 mg q2w (46.5% vs 50.3%, respectively, at week 24). Effect of covariates included the final PopPK/PD model (baseline CRP, physician’s global assessment of disease activity, Health Assessment Questionnaire-Disability Index, body weight, and prior corticosteroid treatment) on PD parameters was small, with no clinically meaningful influences on DAS28-CRP time course.

Conclusions: DAS28-CRP time course after subcutaneous sarilumab administration was described by a semi-mechanistic, indirect-response model, with no clinically meaningful covariates, including body weight and baseline disease activity. Consistent with observed results in clinical studies, the PopPK/PD model showed less reduction in DAS28-CRP after 150 vs 200 mg q2w, thus supporting a starting dose of 200 mg q2w with a decrease to 150 mg q2w in the event of laboratory abnormalities.