**Population Pharmacokinetics and Pharmacodynamics of the Effect of Sarilumab on Absolute Neutrophil Counts in Patients With Rheumatoid Arthritis**

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**Objectives:** Sarilumab is a human mAb blocking the IL-6Ra currently in development for rheumatoid arthritis (RA). Objectives of this analysis were to develop and qualitify a population pharmacokinetic and pharmacodynamic (PopPK/PD) model describing the time course of absolute neutrophil count (ANC) in RA patients and to identify covariates influencing PK/PD relationships using combined data from phase 1 through 3 studies. In sarilumab clinical studies, no relationship between decreases in ANC and infection was identified.

**Methods:** A sequential approach was used: a population pharmacokinetic 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 ANC over time after subcutaneous administrations of sarilumab 50 to 200 mg every week or every 2 weeks (q2w) in 1672 patients. Covariates were evaluated using a stepwise approach. The final PopPK/PD model was evaluated by visual predictive check and bootstrap.

**Results:** ANC time course after sarilumab administration was described by an indirect-response model, linking sarilumab concentrations with ANC via stimulation of ANC elimination rate. Population parameter estimates in the final model translated into a population mean 60% maximal decrease of ANC from baseline, and the population-lowest-possible ANC level was $2.15 \times 10^9$/L with EC$_{50}$ of 10.3 mg/L. Effect on ANC reduction was less (31% reduction from baseline) and fluctuations within each dosing interval were higher for 150 mg q2w than for 200 mg q2w (39% reduction from baseline). The final PopPK/PD model included covariates of smoking status, prior corticosteroids, and body weight on PD parameters. Effect of the above covariates was small, with no clinically meaningful influences on ANC time course.

**Conclusions:** Consistent with observed dose-related ANC reduction in clinical studies, ANC described by an indirect-response model decreased rapidly within 1 to 2 weeks and stabilized 4 weeks after subcutaneous sarilumab administration in RA patients. There was no clinically meaningful influence of the covariates investigated.