Pharmacodynamic (PD) Model of Neutrophil Margination to Describe Transient Effect of Single-Dose Sarilumab on Absolute Neutrophil Count (ANC) in Patients With Rheumatoid Arthritis (RA)

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Objectives: To present a PD model that explains the time course of ANC decrease and recovery, describes neutrophil margination from vascular circulation, and accounts for the rapid development of ANC-specific tolerance.

Methods: In a PK/PD study, 56 patients received a dose of sarilumab 150 or 200 mg SC. Sarilumab concentration and ANC were measured until day 42.

Results: The PD model for ANC values and time course that best described the observed nadir and the return to baseline is a margination model (MM). This MM also describes and accounts for observed tolerance. Margination of ANC, where neutrophils are excluded from the circulation in blood, is a plausible mechanism to describe the transient effect of IL-6 inhibitors on neutrophils without affecting their function. Tolerance accounts for an attenuation of sarilumab effect on ANC over time [1]. Tolerance is manifested by a nadir in ANC that precedes the maximal drug concentrations and by a counterclockwise hysteresis or by the absence of a plateau in the nadir when the ANC response is saturated. This tolerance, being a property limited to the PD effect on ANC, does not affect efficacy. The MM is represented by ANC circulating between central blood and margination compartments. A link function is imposed on the rate from the central to margination compartment. The margination and tolerance are consistent with the absence of impairment in neutrophil activity [2] and lack of association of decrease in ANC and occurrence of infections [3].

Conclusions: A PD model that implements neutrophil margination with ANC-specific tolerance and that describes the mechanism of fast and transient decreases in ANC observed with IL-6 inhibitors has been constructed and describes the data well.