Bridging from the Intravenous to Subcutaneous Formulation of Tocilizumab for Polyarticular Juvenile Idiopathic Arthritis and Systemic Juvenile Idiopathic Arthritis by Leveraging Prior Pharmacometrics Knowledge

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Objectives: To recommend and confirm the subcutaneous (SC) dose regimen of tocilizumab (TCZ) proposed for Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Systemic Juvenile Idiopathic Arthritis (sJIA) using modeling and simulation.

Methods: TCZ is a monoclonal antibody directed against the interleukin-6 (IL-6) receptor. The intravenous (IV) formulation for TCZ was approved for sJIA in 2011 and for pJIA in 2013. The mechanism of action for TCZ is well understood, and the efficacy has shown to be well correlated with the target saturation of IL-6 receptors. The exposure-response relationships between TCZ steady-state C_{trough} ($C_{trough,ss}$) and PD/efficacy parameters were well established for the IV formulation for both pJIA and sJIA. Hence, bridging from IV to SC formulation for TCZ was based on exposure achieved at $C_{trough,ss}$.

Utilizing the population PK models developed for the IV formulation for pJIA and sJIA in combination with prior knowledge on the SC formulation from the adult rheumatoid arthritis population, SC dose regimens that were able to achieve similar ranges of $C_{trough,ss}$ as the IV dose regimen were recommended for pJIA and sJIA.

Interim analyses (IA) were then conducted for the SC studies using the population approach to assess and confirm that $C_{trough,ss}$ achieved by the SC formulation was indeed similar to that achieved by the IV formulation for pJIA and sJIA.

Results/Conclusions: The application of pharmacometrics was critical for the bridge from IV to SC formulation for both pJIA and sJIA. Importantly, IA guided the recommendation of the appropriate SC dose regimens for both indications.

The SC studies are on-going, and the appropriateness of the dose regimens will be confirmed again when the studies are completed. Biomarker data and efficacy/safety responses will also be used to further support the bridging strategy.