Bridging from Intravenous to Subcutaneous Formulation of Tocilizumab for Optimal Dose Regimens in Polyarticular Juvenile Idiopathic Arthritis (pJIA)

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Objectives: To confirm the adequacy of subcutaneous (SC) dose regimens of tocilizumab proposed for pJIA using a pharmacometrics approach.

Methods: Tocilizumab is an IL-6 receptor inhibitor, and the intravenous (IV) formulation was approved for pJIA in 2013. As the exposure-response relationships between steady-state Ctrough (Ctrough,ss) and PD/efficacy parameters are well established for pJIA, bridging from IV to SC TCZ is based on Ctrough,ss. SC regimens 162 mg Q3W (<30kg) and Q2W (≥30kg) were recommended for JIGSAW117, a phase Ib, open-label study with 27 patients <30kg and 25 patients ≥30kg. Serum concentrations from JIGSAW117 were pooled with CHERISH, a randomized, double-blind, placebo-controlled, phase 3 study in 35 patients <30kg (10mg/kg IV Q4W) and 119 patients ≥30kg (8mg/kg IV Q4W). 3484 quantifiable serum samples from 237 pJIA patients were analyzed using a two-compartment model with parallel linear and Michaelis-Menten elimination. Covariate analysis was conducted to identify covariates that may influence disposition of tocilizumab in pJIA patients. Graphical analyses were conducted to evaluate effects of tocilizumab SC exposure on pharmacodynamic biomarkers, key safety parameters, and exploratory efficacy measures.

Results: All pJIA patients in JIGSAW117 achieved Ctrough,ss higher than the 5th percentile achieved with TCZ IV in CHERISH. Observed changes over time in pharmacodynamic biomarkers were similar for both SC regimens. Graphical exposure-safety analyses confirmed there was no apparent association between exposure and occurrence of any SAEs, AEs in “Infections and Infestations” SOC, or grade ≥3 neutropenia AE. Results of graphical exposure-efficacy analyses showed no clear relationship between exposure and Juvenile Arthritis Disease Activity Score 71 and Childhood Health Assessment Questionnaire–Disability Index scores.

Conclusions: Results of these analyses confirmed that tocilizumab 162 mg Q3W (<30kg) and Q2W (≥30kg) regimens are adequate for the treatment of pJIA.