Population Pharmacokinetics and Exposure-Response Analyses for Abatacept in Juvenile Idiopathic Arthritis

X Li,1 JA Passarell,2 K Lin,2 A Roy,1 B Murthy,1 IG Girgis1

1Bristol-Myers Squibb, Princeton, New Jersey 2Cognigen Corporation, a SimulationsPlus Company, Buffalo, New York

Objectives: Abatacept, which inhibits T-cell activation and inflammatory cytokine production, is available in intravenous (IV) and subcutaneous (SC) formulations, and is approved for treatment of adult rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA; 6-17 years [IV] and 2-17 years [SC (US only)]). Population pharmacokinetics (PPK) and efficacy exposure-response (E-R) analyses were conducted to determine whether the proposed weight-tiered SC regimen provided near-maximal efficacy and was therapeutically comparable to the IV regimen in patients with JIA aged 2-17 years.

Methods: Combined data from studies with IV or SC abatacept were analyzed to enable assessment of exposure outcome measures most clinically relevant and applicable to both formulations. The PPK model was developed with data from 13 Phase II/III studies in RA (11 studies; n=2213) and JIA (2-17 years; 2 studies; n=389); the E-R of JIA-American College of Rheumatology (ACR) 30/50/70/100% improvement criteria at Month 4 was characterized by an ordered categorical logistic regression model (data from JIA; 6-17 years; n=357). Predefined relevant covariates were investigated in PPK and E-R analyses. PPK model-predicted exposures evaluated in E-R analysis were: steady-state peak, trough and time-averaged concentrations (C_{maxss}, C_{minss}, and C_{avss}, respectively).

Results: Abatacept PK was characterized by a linear two-compartment model with either zero-order IV infusion or first-order SC absorption, and first-order elimination; only body weight was clinically relevant to exposure. C_{minss} was the best exposure measure for predicting JIA-ACR response: log-odds for response increased in proportion to log-transformed C_{minss}, and JIA-ACR30 approached a plateau for C_{minss} ≥10 µg/mL (Figure). SC weight-tiered doses (50, 87.5 and 125 mg for <20, ≥20 to <50 and ≥50 kg, respectively) achieved C_{minss} (geometric mean [coefficient of variation] 39.7 [35%]) that exceeded the target exposure for near-maximal efficacy.

Conclusions: The PPK and E-R analyses demonstrated that the proposed weight-tiered SC abatacept dosing regimen provides near-maximal efficacy and is therapeutically comparable to the IV abatacept regimen in JIA.

Figure: Cumulative Probability of JIA-ACR Response at Month 4 Versus C_{minss}

The lines represent the model-based predicted probability of JIA-ACR responder. The symbols represent the median C_{minss} of the grouped data and associated observed probabilities. The bars around the symbols represent the standard errors of the observed proportions. The hash marks near the x-axis represent the individual C_{minss} for JIA-ACR responders.