Tofacitinib Dose Selection by Extrapolation of Efficacy from Adult RA to Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Optimal Design to Select PK Sampling Times for a Phase 3 (P3) Study in Children

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Objectives: Select tofacitinib (oral JAK-inhibitor), doses and evaluate/optimize tofacitinib PK sampling windows that reduce patient burden using optimal experimental design (OED) in a P3 pJIA study.

Methods: A nonlinear mixed-effects population PK (POPPK) model was constructed using tofacitinib PK data from 26 pJIA patients (2 to <18yrs, open-label, multiple-dose study). Doses across a wide body weight (BW) range (5-80Kg) were selected based on simulations providing steady state (SS) exposures shown efficacious in RA patients.

OED (method=D-optimality) of the PK-sampling schedule/windows was investigated in PopED. Sampling times were discretized to be consistent with reasonable clinical execution and several sampling windows were evaluated using the efficiency metric based on the determinant of the Fisher information matrix (det(FIM)). Various sampling schemes were evaluated via simulation/re-estimations.

Results: The POPPK model was one-compartment with 1st order absorption. Inter-individual variability (IIV) on CL/F and Ka were described by exponential error models. Power coefficients (mean[95% CI]) relating BW to CL and V/F were 0.292[0.125-0.525] and 0.843[0.621-0.993], respectively. Figure 1 displays simulated tofacitinib Cavg,SS,pJIA (relevant exposure metric for efficacy in RA), across a BW range (5-80kg) for the proposed P3 dosing regimen in pJIA.

Substantial difference in det(FIM) was observed when comparing 2 vs. 3 sampling times and differing terminal sampling times. Final design provided the highest expected efficiency conditional on clinical execution constraints (sample number and clinic visit-time) at 0.25 hr±5min, 0.75 hr±10min, 3h[-15min;+30min]. Relative root mean squared errors were 13.77% and 14.24% for CL/Ftofacitinib,pJIA and V/Ftofacitinib,pJIA, respectively.

Conclusions: Selected tofacitinib-doses for pJIA patients with BW <40 kg were based on BW while for BW >40 kg were capped at 5mg BID. Predicted concentrations at these proposed doses were equivalent to those of adult RA doses of 3-5mg BID. Implementation of OED allowed sample number reduction and shortened stay duration at investigator sites.

Figure 1