Population Pharmacokinetics and Exposure-Response Analysis of Entospletinib, a Selective Spleen Tyrosine Kinase Inhibitor

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Objectives: Entospletinib (ENTO) is an orally bioavailable, selective, reversible, small molecule spleen tyrosine kinase inhibitor. ENTO is currently in a Phase 2 clinical trial in patients with relapsed or refractory CLL/NHL. The objective was to develop a population pharmacokinetic model for ENTO and investigate the exposure-efficacy relationship.

Methods: In healthy volunteers (N=96, HV), ENTO (25 mg to 1200 mg) was orally administered as single or multiple (once daily or twice daily) ascending doses. In subjects with hematological malignancies (N=142), ENTO 800 mg twice daily was administered and pharmacokinetic samples were collected on Cycle 1 Day 1 (pre-dose, 1.5 and 4 hours post-dose) and subsequent cycles (pre-dose). A nonlinear mixed-effects model was fitted to ENTO plasma concentrations. Covariates screened for influence on ENTO PK were baseline body weight, BMI, BSA, age, creatinine clearance, AST, ALT, bilirubin, sex, race and disease status (HV versus patient). Relationships between model predicted ENTO exposures and early efficacy end points such as tumor size (SPD), overall response rate (ORR) and best overall response (BOR) were evaluated.

Results: A two-compartment model with dose dependent, non-linear absorption and first order elimination described ENTO PK, based on visual predictive check and parameter estimate precision. ENTO PK was unaffected by the baseline covariates evaluated. ENTO exposures (AUC, Cmax and Ctrough) were comparable between HVs and patients (CLL or FL). Over the range of ENTO exposures (~3 to 4 fold range between midpoint of first vs fourth quartile), no association was observed with SPD, ORR or BOR for either CLL or FL population.

Conclusions: ENTO PK is unaffected by demographic, biometric, or disease-relevant covariates. No relevant relationship between exposure and early efficacy in a limited subset of patients was observed, suggesting that ENTO 800 mg BID provided exposures resulting in consistent therapeutic effects.