**Population PK/PD Modeling for Evaluation of Filgotinib Efficacy in Subjects with Moderate to Severe Crohn’s Disease**

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**Objectives**: Filgotinib (FIL) is a potent and selective inhibitor of JAK1, which is a therapeutic target for a range of inflammatory conditions including Crohn’s Disease (CD). Severity of CD is assessed by the Crohn’s Disease Activity Index (CDAI) score. A PK/PD model describing the progression of CDAI was developed to evaluate the exposure-efficacy relationship for FIL in CD patients.

**Methods**: In a Phase II study, subjects received 200mg FIL (N=128) or placebo (N=44) during first 10 weeks. Subsequently, based on Week 10 efficacy outcome, subjects were re-assigned to receive 200mg, 100mg FIL or placebo through Week 20. Population PK of FIL has been characterized previously. Total systemic exposure (AUC\(_{\text{tau}}\)) was incorporated to account for drug effect. PK/PD (CDAI score progression) analysis was conducted with NONMEM® v7.3 and R v3.3.2 used for processing/visualizing data.

**Results**: CDAI score progression was characterized by a bi-exponential function:

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\text{CDAI} = \text{BL} \times (1 + \text{PLC} \times (1 - e^{k1 \times \text{TIME1}} - e^{k2 \times \text{TIME2}})),
\]

where BL was the baseline, PLC was the magnitude of placebo effect, k1 was the onset rate constant described as \(k_{\text{pl}} \times (1 + \text{slope} \times \text{AUC})\), k2 was the relapse rate constant, \text{TIME1} was time since first dose and \text{TIME2} was time to relapse. The final model estimates (rse\%) were -0.793 (3\%) for PLC, 0.0169/day (12\%) for \(k_{\text{pl}}\), 0.0142/day (11\%) for \(k_2\), and 0.0262 mL/(ng*h) (54\%) for slope of drug effect. Inter-individual variability (%CV) was 106\% on \(k_{\text{pl}}\), 184\% on slope, 45.2\% for time when relapse occurs and 13.5\% for BL.

Diagnostics showed that the model adequately described the observed CDAI scores.

**Conclusions**: The PK/PD model characterized the progression of CD, and captured drug effect across different FIL treatment arms of the phase II study. This model can be applied to simulate various treatment paradigms for FIL in subjects with CD.