Population pharmacokinetics and exposure-response of filgotinib in patients with moderate to severe Crohn’s disease

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Objectives: Filgotinib (FIL), a selective janus kinase-1 (JAK-1) inhibitor, has shown a favorable benefit-risk profile in patients with moderate to severe Crohn’s disease (CD). The objective was to develop a population pharmacokinetic (PK) model and investigate the exposure-response (efficacy/safety) relationship.

Methods: In a Phase 2, double-blind study, CD patients (N=143) were administered FIL (200 mg versus placebo, once daily [QD]) for 10 weeks. Sparse and intensive PK sampling for FIL and its active metabolite (MET) was performed. Nonlinear mixed-effects models were fitted to FIL/MET plasma concentrations. Covariates screened for influence on FIL/MET PK were baseline age, weight, height, BMI, BSA, sex, race, study region and creatinine clearance. Relationships between model predicted FIL/MET exposures and efficacy (clinical response, remission, endoscopic response) and safety (such as blood count and lipid profile) assessments at Week 10 (primary end point visit), following FIL 200 mg QD, were evaluated.

Results: FIL PK were described by a two-compartment model with first-order absorption, first-order elimination, and a lag time. MET PK were described by a one-compartment model with first-order absorption, first-order elimination, and a lag time. None of the covariates showed a statistically significant effect on FIL/MET PK. The population mean (%IIV) estimate of FIL CL/F was 107.9 (110%) L/hr, Vc/F was 4.17 (139%) L and Ka was 0.18 (72%) 1/h. The population mean (%IIV) of MET CL/F was 3.48 (34%) L/hr, Vc/F was 199.3 (58%) L and Ka was 0.73 (77%) 1/hr. Over the range of FIL/MET exposures (divided into quartiles; > 2 fold range between midpoint of first vs fourth quartile) following FIL 200 mg QD, no association with efficacy or safety was observed.

Conclusions: FIL/MET PK is unaffected by demographic or disease-relevant covariates. No relevant relationship between FIL/MET exposure and efficacy/safety was observed, suggesting that FIL 200 mg QD provided consistent therapeutic effects without any adverse exposure-driven safety trends in CD patients.