Mechanistic Population Pharmacokinetics Model of PF-00547659, a Full Human IgG2 anti-MAdCAM Monoclonal Antibody in Ulcerative Colitis Patients

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Objectives: Characterize the pharmacokinetics (PK) of PF-00547659 in ulcerative colitis (UC) patients and identify clinical relevant covariates.

Methods: One phase 1/2a and 1 phase 2 studies with a total of 363 subjects with 2476 serum concentrations were included in the analysis. The Phase 1/2a study included single or multiple (MD) intravenous (IV) or subcutaneous (SC) dosing every 4 weeks up to 8 weeks with doses ranging from 0.03 to 10mg/kg. The ongoing phase 2 study utilized MD SC dosing from 7.5mg to 225mg. The PK analysis was conducted using the nonlinear mixed-effects modeling.

Results: The PK of PF-00547659 in UC patients was best described by a two compartment model incorporating first-order SC absorption; with elimination combining linear and a nonlinear pathway binding to mucosal addressing cell adhesion molecule (MAdCAM) and subsequent internalization and elimination of the complex (termed target mediated drug disposition, TMDDref). Covariates identified were baseline body weight (BWT), baseline albumin (BALB), and baseline CRP (BCRP) on linear antibody clearance (CL), and BWT on central compartment volume (V1). For a typical patient (BWT of 73kg, BALB of 3.9g/dL and BCRP of 0.52mg/dL), linear CL was estimated to be 8.43mL/h (half-life=21days) with central and peripheral compartment volumes of 3.34L and 2.2L, respectively. The production, degradation rates (assumed same as complex) of MAdCAM, and Kd were 0.0706nmol/h, 43.2mL/h, and 0.396nmol/L, respectively. TMDD was fully saturated at doses ≥75mg/month.

Conclusions: The pharmacokinetics of PF-00547659 was typical of a monoclonal antibody with TMDD observed at low doses. PF-00547659 remained primarily within the vasculature near its target site. Following SC dosing of 22.5 mg every four weeks, the model predicted an average suppression of >90% in free MAdCAM in UC patients.

References: S.W.Martin, et al (2009) AGA Digestive Disease Week, Chicago IL.