Population Pharmacokinetic Analysis of Dupilumab Using Early Phase and Phase 3 Data

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Objectives: To estimate the population and individual PK parameters of functional dupilumab across an array of studies and populations and explore clinically-relevant covariates.

Methods: The data included 13 phase 1 and 2 studies and 3 phase 3 studies in healthy volunteers and patients with atopic dermatitis (AD). A stepwise approach was used to build the base model, with some parameters estimated using mostly rich data from early clinical studies and subsequently fixed. The model was parameterized in terms of micro constants to minimize the number of repetitive significant covariates. Forward inclusion and backward elimination was used to select covariates. Stochastic approximation expectation-maximization and importance sampling methods were utilized for parameter estimation.

Results: A two-compartment PK model with parallel linear and Michaelis-Menten elimination, and with three transit compartments accounting for lag time after subcutaneous injection, was implemented. Parameters were: central volume \( (V_c) \) 2.74 L, elimination rate \( (k_e) \) 0.0477 d\(^{-1}\), central-to-peripheral rate \( (k_{cp}) \) 0.211 d\(^{-1}\), peripheral-to-central rate \( (k_{pc}) \) 0.310 d\(^{-1}\), bioavailability \( (F) \) 64.2%, maximal target-mediated elimination rate \( (V_m) \) 1.07 mg/L/d, Michaelis–Menten constant \( (K_m) \) 0.01 mg/L, absorption rate \( (k_a) \) 0.256 d\(^{-1}\), and mean transit time \( (MTT) \) 0.105 d\(^{-1}\); \( k_e, k_{cp}, k_{pc}, k_a, V_m, K_m, \) and \( F \) were estimated using selected early phase studies and fixed when phase III data were analyzed; as the target-mediated phase was steep, \( K_m \) was estimated using profiling. Only weight had a noticeable effect on between-subject variability.

Conclusions: A two-compartment PK model implementing parallel linear and Michaelis-Menten elimination and transit compartments adequately described the PK of dupilumab in healthy volunteers and AD patients. Only weight had a noticeable effect on \( V_c \), explaining between-subject variability. None of the covariates had a sufficient effect on dupilumab exposure that warrants dose adjustment.