

Population Pharmacokinetics of AMG 317, a Fully Human Anti-IL-4R α IgG2 Monoclonal Antibody Evaluated in Healthy and Asthmatic Subjects

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Purpose.

To investigate the population pharmacokinetics (PK) of AMG 317.

Methods.

The dataset included 2184 AMG 317 concentrations from 295 subjects of 12 to 64 years old weighing 44 to 256 kg. Of them, 58% were males and 84% were asthmatic patients. Also, 9.8% were administered single IV doses ranging from 10 to 1000 mg, and 90.2% were administered single or multiple (up to 12 weeks of once-weekly) SC doses ranging from 30 to 600 mg. Doses were administered as 30 or 100 mg/mL solution. The population PK analysis was conducted via nonlinear mixed-effects modeling with Nonmem VI.

Results.

A two-compartment model with quasi-steady-state (QSS) approximation of the target-mediated drug disposition described AMG 317 PK. Central volume, clearance, inter-compartmental clearance, and peripheral compartment volume for a typical subject (WT=80 kg, AGE=40 years, SC administration) were estimated as $V_2=2100$ (95% CI: 1760-2270) mL, $CL=41.3$ (36-45) mL/hr, $Q=30.2$ (26.2-33.8) mL/hr, and $V_3=6150$ (5300-6840) mL, respectively. The total receptor concentration was estimated as $R_{max}=296$ (249-331) ng/mL. The QSS constant was estimated as $K_{SS}=45$ (36-55) ng/mL, similar to in-vitro dissociation constant ($K_D=27$ ng/mL). Bioavailability of the SC formulation was estimated as $F_1=28.2$ (24.4-29.7) %. Absorption was slow, with half-life $t_{1/2}=3.4$ (3.3-4.4) days. Central volume following IV administration was estimated as 70 (52-99)% higher than following SC administration. The inter-subject variability of CL, Q, V_2 , and KA was moderate, ranging from 33 to 41%. An allometric model for linear clearance and central volume described the dependence of parameters on body size measures. Absorption rate decreased with age. It was 36 (27–80) % higher for a 20-year old and 17 (13-29)% lower for a 60-year old, respectively, than for a 40-year old subject. AMG317 concentrations were slightly lower in subjects with detected anti-AMG317 antibodies, but results do not indicate any significant and unexplained decline in the observed concentrations for these subjects.

Conclusion.

The population PK model was able to adequately describe AMG 317 pharmacokinetics in the entire range of available doses with 2 dosing strengths, across multiple studies covering healthy volunteers and subjects with different severities of asthma, routes of administration, weight and age ranges.

[Return to the Main Page](#)

[Return to the Publication Page](#)