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Population Pharmacokinetics of AMG 317, a Fully Human Anti-IL-4Rα IgG2 Monoclonal Antibody Evaluated in Healthy and Asthmatic Subjects	
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Poster: Applications- Biologicals/vaccines	

Background: AMG 317 is a fully human IgG_2 monoclonal antibody that was tested as a treatment for asthma based on its potent ability to block both IL-4 and IL-13 activity in-vitro by binding to IL-4Rα.

Objectives: To investigate the population PK of AMG 317 following subcutaneous and intra-venous administration of AMG 317 in healthy and asthmatic subjects.

Methods: The population PK analysis was conducted via nonlinear mixed-effects modeling with the Nonmem VI 2.0. The first-order conditional estimation method with interaction option (FOCEI) was employed for all model runs. The final model was evaluated using the diagnostic plots, bootstrap analysis, and predictive check simulations.

Results: The dataset included 2184 AMG 317 concentration values from 295 subjects. Among 291 subjects with available covariate information, there were 169 males and 122 females. The median (range) age and weight were 36 (12 - 64) years and 83 (44 - 256) kg. There were 9 patients with weight > 140 kg; 248 asthmatic patients (84.1%) and 47 healthy volunteers (15.9%). AMG 317 was administered as an IV bolus or infusion to 29 subjects (9.8%) and as a SC injection to 266 subjects (90.2%). The IV doses ranged from 10 to 1000 mg, while the SC doses ranged from 30 to 600 mg.
A two-compartment model with the target-mediated drug disposition (TMDD) described the PK of AMG 317 [1, 2]. The Michaelis-Menten (MM) approximation with parallel linear and nonlinear elimination routes was sufficient to describe the concentration-time data that were above the 300 ng/mL level. The quasi-steady-state (QSS) approximation of the TMDD model adequately described the entire range of the observed data.
AMG 317 central volume and clearance for a typical subject (WT=80 kg, AGE=40 years, SC administration) were estimated as V2 = 2100 mL (95%CI: 1760 - 2270 mL) and CL = 41.3 mL/hr (95%CI: 36 - 45 mL/hr), respectively. Inter-compartmental clearance Q and peripheral compartment volume were estimated at 30.2 L/hr (95%CI: 26.2 - 33.8 mL/hr) and 6150 mL (95%CI: 5300 - 6840 mL), respectively. The total receptor concentration (RMAX) was estimated at 296 ng/mL (95% CI: 249 - 331 ng/mL) that is close to the lower limit of the concentration range where the concentration-time data are well-described by the MM model. QSS constant KSS was estimated at 45 ng/mL (95% CI: 36 - 55 ng/mL), in agreement with the value of the AMG 317 dissociation constant (KD=1.8*10-10 M or about 27 ng/mL).
Bioavailability of the SC formulation was estimated at 28.2% (95% CI: 24.4 - 29.7%). Absorption was slow, with the absorption half-life of 3.4 days (95% CI: 3.3 - 4.4 days). Central volume following IV administration was estimated to be 70% (95%CI: 52 - 99%) higher than central volume following SC administration. The inter-subject variability of CL, Q, V2, 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% higher (95%CI: 27 – 80%) for a 20-year old and 17% lower (95%CI: 13 - 29%) for a 60-year old, respectively, than for a 40-year old subject. AMG 317 concentrations were slightly lower in subjects with detected anti-AMG 317 antibodies, but results do not indicate any significant and unexplained decline in the observed AMG 317 concentrations for these subjects.

Conclusions: Population PK model was able to adequately describe AMG317 pharmacokinetics in the entire range of available doses, routes of administration, weight and age ranges.

References:
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[2] Gibiansky L, Gibiansky E, Kakkar T, Ma P: Approximations of the target-mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn. (2008) 35(5):573-91

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