Population Pharmacokinetics of AMG317, a Fully Human Anti-IL-4Ra IgG2 Monoclonal Antibody Evaluated in Healthy and Asthmatic Subjects

Tarundeep Kakkar1, Leonid Gibiansky2, Peiming Ma1
1Amgen Inc., Thousand Oaks, CA, US; 2QuantPharm LLC, North Potomac MD, USA

ABSTRACT

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

METHODS

A two-compartment model with quasi-steady-state (QSS) approximations of the target-mediated drug disposition described AMG 317 PK. Central volume, inter-compartmental clearance, and peripheral compartment volume for a typical subject (WT=80 kg, AGE=40 years, SC administration) were estimated as QSS=2 (0.9-4) mL/hr, C=0.3 (0.2-0.4) mg/L, k12=3.3 (2.0-5.6) mg/L, k21=2.2 (1.2-3.7) mg/L, respectively. The total receptor concentration was estimated in range [200-290 (209-331)] ng/mL. The QSS constant was estimated as QA=45 (35-55) ng/mL, similar to in vitro dissociation constant (Ki=27 ng/mL), linearity of AMG 317 PK and state (QSS) behavior. AMG 317 concentrations were slightly lower in subjects with 30.2 (26.2-33.8) mL/hr, and V3 6150 (5300-6840) mL respectively. The total receptor concentration; K0 0.562 (0.421-0.71) mg/L, t1/2 3.4 (3.3-3.5) days. Central volume following IV administration was estimated at QSS=0.9 (0.7-1.2) mL/kg, higher than following SC administration. The inter-subject variability of CL, Q, V2, and FA was reduced, ranging from 35% 4% respectively. An allometric model for linear clearance and central volume was developed describing a weight-based dose regimen. Absorption rate decreased with weight model for CL and KSS=45 (36-55) ng/mL was in agreement with the in vivo data described by AMG 317 PK and state (QSS) behavior.

RESULTS

A two-compartment 1M4L model (QSS or MM approximations); QA 30.2 (26.2-33.8) mL/hr, and V3 6150 (5300-6840) mL respectively. The total receptor concentration was slightly lower in subjects with 0.562 (0.421-0.71) mg/L, t1/2 3.4 (3.3-3.5) days. Central volume following IV administration was estimated at QSS=0.9 (0.7-1.2) mL/kg, higher than following SC administration. The inter-subject variability of CL, Q, V2, and FA was reduced, ranging from 35% 4% respectively. An allometric model for linear clearance and central volume was developed describing a weight-based dose regimen. Absorption rate decreased with weight model for CL and KSS=45 (36-55) ng/mL was in agreement with the in vivo data described by AMG 317 PK and state (QSS) behavior.

CONCLUSIONS

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.

OBJECTIVES

• To develop and evaluate a population model that describes AMG 317 pharmacokinetics in the entire range of available doses, routes of administration, weight and age ranges.
• To investigate AMG 317 pharmacokinetics following SC and IV administrations in healthy and asthmatic subjects.

REFERENCES