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

Tarundeep Kakkar[1], Leonid Gibiansky[2], Peiming Ma[1]

[1]Amgen Inc., Thousand Oaks, CA, US; [2]QuantPharm LLC, North Potomac MD, USA

ABSTRACT

Purpose.
To investigate the population pharmacokinetics (PK) of AMG 317.
Methods.
The dataset included 2184 AMG 317 concentrations from 295 subjects; age ranging from 12 to 64 years and 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 V2=2100 (95%CI: 1760-2270) mL, CL=41.3 (36-45) mL/hr, Q=30.2 (26.2-33.8) mL/hr, and V3=6150 (5300-6840) mL, respectively. The total receptor concentration was estimated as Rmax=296 (249-331) ng/mL. The QSS constant was estimated as KSS=45 (36-55) ng/mL, similar to in-vitro dissociation constant (KD=27 ng/mL). Bioavailability of the SC formulation was estimated as F1=28.2 (24.4-29.7) %. Absorption was slow, with half-life t1/2=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, 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 (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. 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 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.

BACKGROUND

- A fully human IgG2 monoclonal antibody with potent ability to block IL-4 and IL-13 activity in-vitro by binding to IL-4Rα;
- Tested as a treatment for asthma in four Phase 1-2 studies;
- 295 subjects with single IV doses of 10-1000 mg, and single or multiple SC doses of 75-600 mg;
- The drug exhibits target-mediated pharmacokinetics.

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 administration in healthy and asthmatic subjects.

METHODS

- Nonlinear mixed-effects modelingwas performed with Nonmem VI 2.0;
- FOCEI method was employed for all model runs;
- Quasi-Steady-State (QSS) and Michaelis - Menten (MM) models [1, 2] were employed to describe target-mediated drug disposition (TMDD) behavior;
- Full-model covariate modeling approach was implemented;
- Model evaluation was performed through diagnostic plots, stratified bootstrap analysis, and predictive check simulations.

RESULTS

- A two-compartment TMDD model (QSS or MM approximations);
- The MM model with parallel linear and MM elimination described the data above 300 ng/mL;
- The QSS model described the entire range of the observed data:

$$C = \frac{1}{2}\left[(C_{tot} - R_{max} - K_{SS}) + \sqrt{(C_{tot} - R_{max} - K_{SS})^2 + 4K_{SS}C_{tot}}\right];$$

$$\frac{dA_1}{dt} = -k_a A_1;$$

$$\frac{dA_2}{dt} = F_{SC}k_a A_1 - k_{int}A_2 - (CL - k_{int}V_c)C - QC + QA_3/V_p;$$

$$\frac{dA_3}{dt} = QC - QA_3/V_p.$$

Here R_{max} is the total receptor concentration; K_{SS} is QSS constant; k_{int} is internalization (elimination of the drug-receptor complex) rate constant; A_1, A_2 and A_3 are the drug amounts in the depot, central and peripheral compartments, respectively, and $C_{tot}=A_2/V_c$ and C are the total and free AMG 317 plasma concentrations, respectively.

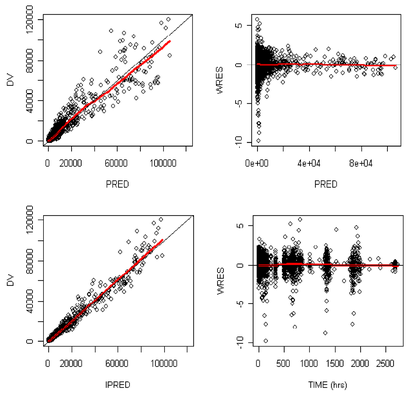
- The parameters of the model (Table 1) indicated:
  - ✓ R_{max}=296 ng/mL was close to the lower limit of the concentration range where the data were well-described by the MM model. This is consistent with the notion that MM model should only be able to describe concentrations that are much higher than R_{max};
  - ✓ $K_{SS}=K_D+k_{int}/k_{on}$=45 ng/mL was in agreement with the in-vitro dissociation constant value K_D= 27 ng/mL;
  - ✓ Bioavailability of the SC formulation was estimated at 28.2% ;
  - ✓ Slow absorption with absorption half-life of 3.4 days (95% CI: 3.3 - 4.4 days);
  - ✓ V_c following IV dose was 70% higher than V_c following SC dose;
  - ✓ Allometric weight model for CL and V_c ;
  - ✓ Absorption rate decreased with age.
- AMG 317 concentrations were slightly lower in subjects with anti-AMG 317 antibodies, but there was no significant and unexplained decline in the observed concentrations for these subjects.

RESULTS

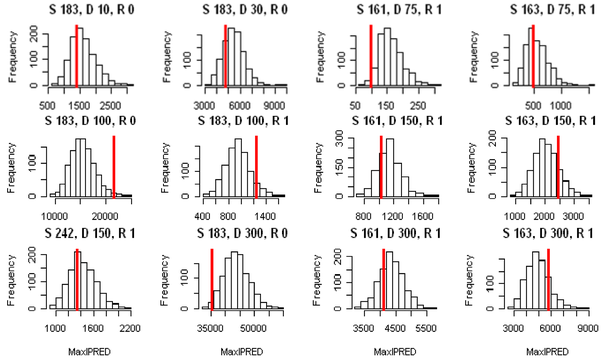
Table 1. Population Parameters of the Final Population PK Model

Parameter	Value	Bootstrap Median (95% CI)	Variability	Shrinkage
CL (mL/hr)	41.3	41.2 (36 ; 45)		
V_c (mL)	2100	2080 (1760 ; 2270)		
V_p (mL)	6150	6130 (5300 ; 6840)		
Q (mL/hr)	30.2	29.9 (26.2 ; 33.8)		
K_{SS} (ng/mL)	45	44.5 (36.2 ; 55.3)		
k_{int}(1/hr)	0.17	0.171 (0.155 ; 0.203)		
R_{max} (ng/mL)	296	295 (249 ; 331)		
k_a(1/hr)	0.00853	0.00831 (0.00662 ; 0.00876)		
F_{SC}	0.282	0.278 (0.244 ; 0.297)		
$k_{a,AGE}$	-0.447	-0.508 (-0.844 ; -0.349)		
$V_{2,FORM}$	0.568	0.562 (0.421 / 0.737)		
V_{IV}	1.7	1.71 (1.52 ; 1.99)		
$\omega^2_{CL}=\omega^2_Q$	0.166	0.17 (0.136 ; 0.233)	CV=40.8%	22.4%
ω^2_{Vc}	0.107	0.104 (0.0755 ; 0.125)	CV=32.7%	20.5%
ω^2_{ka}	0.159	0.14 (0.0958 ; 0.214)	CV=39.8%	31.4%
σ^2_{add}	985	1010 (725 ; 2530)	SD=31.4	
σ^2_{exp}	0.0646	0.0632 (0.0479 ; 0.0677)	CV=25.4%	

Basic Diagnostic Plots

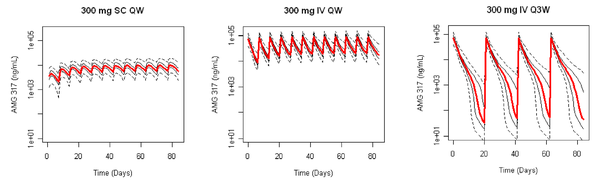


Predictive check simulations: distributions of simulated medians of Cmax by study, dose and route of administration



Simulated AMG 317 Concentrations Following 12 Weeks of 300 mg SC QW, 300 mg IV QW, 300 mg IV Q3W, Semi-Log Scale

Red: Median: Solid black: 25th and 75th percentiles: Dashed black: 5th and 95th percentiles.



CONCLUSIONS

The population PK QSS model adequately described pharmacokinetics of AMG 317 in the entire range of available doses, routes of administration, weights and ages.

REFERENCES

[1] Mager DE, Krzyzanski W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Pharm. Res, 22 (10), 2005.

[2] Gibiansky L, Gibiansky E, Kakkar T, Ma P, Approximations of the Target-Mediated Disposition Model and Identifiability of Model Parameters, JPP 35(5) 2008.

AMGEN QUANTPHARM