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

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PAGE 2009, June 23-26, St. Petersburg, Russia

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;
- Was tested as a treatment for asthma in four Phase 1-2 studies;
- 295 subjects with single IV doses of 10 to 1000 mg; single or multiple SC doses 75 to 600 mg;
- Target-mediated pharmacokinetics.

OBJECTIVES:

- To investigate AMG 317 population PK following SC and IV administration in healthy and asthmatic subjects.

DATA:

- 2184 concentration values from 295 subjects.
- 291 subjects with available covariate information:
  - ✓ 169 males and 122 females;
  - ✓ The median (range) age: 36 (12 - 64) years;
  - ✓ The median (range) weight: 83 (44 - 256) kg (9 patients over140 kg);
  - ✓ 248 (84.1%) asthmatic and 47 (15.9%) healthy;
  - ✓ IV 10-1000 mg bolus or infusion to 29 (9.8%) subjects;
  - ✓ SC 75 – 600 mg injection to 266 (90.2%) subjects.

METHODS:

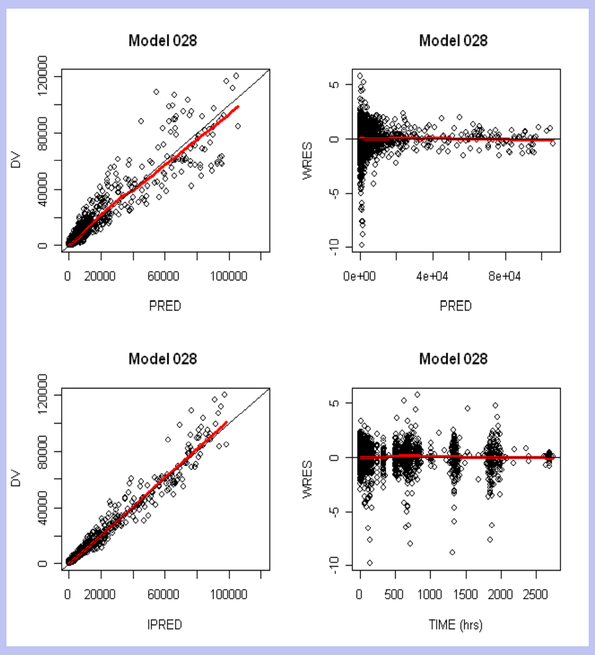
- Nonlinear mixed-effects modeling with Nonmem VI 2.0;
- FOCEI was employed for all model runs;
- Target-mediated drug disposition (TMDD): Quasi-Steady-State (QSS) and Michaelis - Menten (MM) models [1, 2];
- Full-model covariate modeling approach;
- Model evaluation using the diagnostic plots, stratified bootstrap analysis, and predictive check simulations.

RESULTS:

- A two-compartment TMDD model (QSS or MM approximations);
- MM model with parallel linear and MM elimination described the data above the 300 ng/mL;
- QSS model described the entire range of the observed data;
- Parameters of the model are presented in Table 1:
  - ✓ 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 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 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.

MODEL VALIDATION:

Basic Goodness-of-fit Plots and dependencies of individual random effects versus age, weight, and route



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

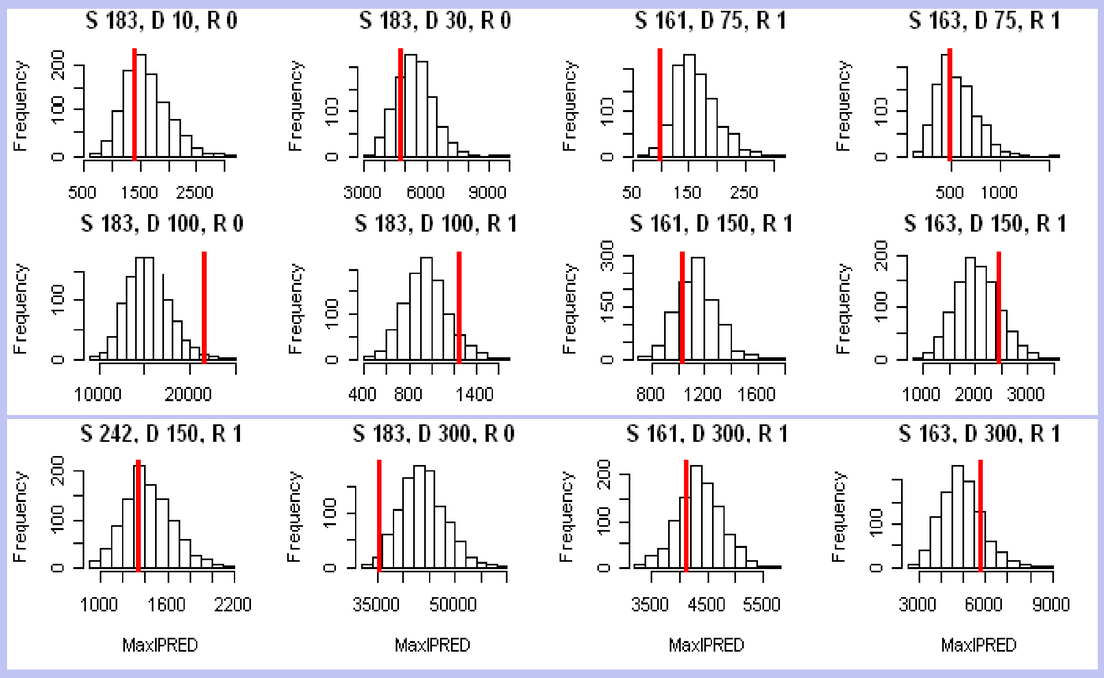


Table 1. The Population Parameters of the Final Population PK Model

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)		
ω^2_{CL}=ω^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%	

CONCLUSIONS

- Population PK QSS model adequately described AMG317 PK in the entire range of available doses, routes of administration, weight and age ranges.

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.