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

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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 over 140 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;
- FOCE1 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_{eff}+k_{on}/k_{off}=45 ng/mL was agreement with the in-vitro dissociation constant value k_{off}=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.

REFERENCE:

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 C_{max} by study, dose and route.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Bootstrap Median (95% CI)</th>
<th>Variability</th>
<th>Shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (mL/hr)</td>
<td>41.3</td>
<td>41.2 (36.4 - 45.7)</td>
<td>22.4%</td>
<td>20.5%</td>
</tr>
<tr>
<td>V_C(mL)</td>
<td>2100</td>
<td>2080 (1960 - 2270)</td>
<td>25.4%</td>
<td>23.6%</td>
</tr>
<tr>
<td>V_R(mL)</td>
<td>6150</td>
<td>6130 (5100 - 6840)</td>
<td>26.7%</td>
<td>24.9%</td>
</tr>
<tr>
<td>Q (mL/hr)</td>
<td>30.2</td>
<td>29.9 (26.2 - 33.6)</td>
<td>27.8%</td>
<td>25.9%</td>
</tr>
<tr>
<td>k_{SS} (ng/mL)</td>
<td>45</td>
<td>44.3 (36.2 - 55.3)</td>
<td>28.9%</td>
<td>26.4%</td>
</tr>
<tr>
<td>k_{eff} (hr^{-1})</td>
<td>0.17</td>
<td>0.171 (0.155 - 0.203)</td>
<td>29.1%</td>
<td>27.3%</td>
</tr>
<tr>
<td>R_{max} (ng/mL)</td>
<td>296</td>
<td>295 (249 - 331)</td>
<td>30.2%</td>
<td>28.5%</td>
</tr>
<tr>
<td>k_{off} (hr^{-1})</td>
<td>0.00583</td>
<td>0.00581 (0.00562 - 0.00586)</td>
<td>31.2%</td>
<td>29.5%</td>
</tr>
<tr>
<td>V_C (mL)</td>
<td>1090</td>
<td>1090 (1025 - 1156)</td>
<td>32.1%</td>
<td>30.3%</td>
</tr>
<tr>
<td>V_R (mL)</td>
<td>985</td>
<td>985 (910 - 1060)</td>
<td>33.1%</td>
<td>31.4%</td>
</tr>
</tbody>
</table>

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

Return to the Publications page
Return to the main page