How can modeling and simulation optimize the clinical development of adalimumab biosimilar candidates?

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RATIONALE

- The number of subjects required for a desired power depends on the magnitude of the variability.
- Adalimumab displays large variability, which should considered when assessing PK similarity.
- An adalimumab population PK model, incorporating PK altering factors (formulation sources, anti-adalimumab neutralizing antibodies), subjects variability (body weight) and residual uncertainty can guide the optimal design of such trials.
- The probability of concluding PK similarity was evaluated through extensive model-based simulations, keeping all statistical assumptions the same as for the traditional method.

MODEL

Parameter estimates were obtained for adalimumab-EU/US using a literature PK model. There was good agreement between observations and predictions (Figure 1).

![Model predictions for adalimumab public domain data (EU/US).](image)

Figure 1. Model predictions for adalimumab public domain data (EU/US).

MODEL QUALIFICATION

PK model from the literature was deemed appropriate to describe adalimumab-EU/US comparison (Table 1).

<table>
<thead>
<tr>
<th>Source</th>
<th>US geometric mean ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>AUClast</td>
</tr>
<tr>
<td>adalimumab-EU/US from Literature PK model</td>
<td>0.994 (0.884; 1.118)</td>
</tr>
<tr>
<td>adalimumab-EU/US from ABP 501 study</td>
<td>1.083 (N.R)</td>
</tr>
<tr>
<td>adalimumab-EU/US from S55 study</td>
<td>1.036 (0.920; 1.121)</td>
</tr>
</tbody>
</table>

Table 1. Model qualification for adalimumab PK model.

PROBABILITY OF CONCLUDING PK SIMILARITY

A sample size of 140 subjects provided at least 0.91 probability to conclude similarity for all three pair-wise comparisons of AUCinf. The probability to conclude similarity for AUClast was approximately the same as that for AUCinf. Despite the high variability, Cmax showed good probability to pass PK similarity for all pairwise comparisons but lower for EU vs US with a CV% > 30 (Table 2).

<table>
<thead>
<tr>
<th>Source</th>
<th>Cmax</th>
<th>AUCinf</th>
<th>AUClast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization 1:1:1</td>
<td>N=120</td>
<td>N=140</td>
<td>N=133</td>
</tr>
<tr>
<td>EU/US</td>
<td>0.5</td>
<td>0.850</td>
<td>0.853</td>
</tr>
<tr>
<td>EU/US</td>
<td>0.803</td>
<td>0.865</td>
<td>0.945</td>
</tr>
<tr>
<td>EU/US</td>
<td>0.812</td>
<td>0.899</td>
<td>0.945</td>
</tr>
<tr>
<td>Randomization 1:1:1</td>
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<td>N=140</td>
<td>N=133</td>
</tr>
<tr>
<td>EU/US</td>
<td>0.5</td>
<td>0.835</td>
<td>0.772</td>
</tr>
<tr>
<td>EU/US</td>
<td>0.805</td>
<td>0.857</td>
<td>0.927</td>
</tr>
<tr>
<td>EU/US</td>
<td>0.19</td>
<td>0.819</td>
<td>0.935</td>
</tr>
</tbody>
</table>

Table 2. Probability of concluding PK similarity.

CONCLUSIONS

- The population PK literature model was suitable to describe the plasma concentration time-course of EU- and US-approved adalimumab in healthy subjects after single 40 mg s.c. administration.
- Compared with traditional adalimumab biosimilar PK trials using 200-300 subjects, the simulations indicate the sample size can be reduced by 40-60% maintaining the chance to detect differences in all pairwise comparisons (90%CI) above 80%.