APG777, a high-affinity humanized IgG1 mAb targeting IL-13, demonstrates prolonged half-life in non-human primates

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Introduction

IL-13 signaling begins with binding of IL-13 to IL-13Rα1. This forms an inactive complex that then binds to IL-4Rα to create a complete, active heterodimer. IL-13 signaling is well-absorbed, with subcutaneous F determined to be 81.22% (Table 1).

Materials and methods

- The pharmacokinetics of APG777 and a monoclonal antibody expressed based on the published sequence of lebrikizumab were studied in female cynomolgus monkeys following a single bolus dose of 3 mg/kg, given either intravenously (IV) or subcutaneously (SC).
- Blood samples were collected serially starting with a pre-dose and subsequently at 0.167, 1, 4, 8, 24, 48, 96, 168, 336, 504, 674, 840, 1334, 1680, and 2160 hours post-dose.
- Pharmacokinetic parameters included:
  - Maximum observed serum concentration (Cmax).
  - Area under the serum concentration versus time curve from time 0 extrapolated to infinity (AUC0-inf).
  - Clearance (Cl).
  - Volume of distribution at steady-state (Vss).
  - Absolute subcutaneous bioavailability (F).
  - Time to maximum observed serum concentration (Tmax).

Table 1: Pharmacokinetics of APG777 and lebrikizumab following a single bolus IV or SC dose in cynomolgus monkeys

<table>
<thead>
<tr>
<th></th>
<th>APG777</th>
<th>Lebrikizumab*</th>
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<tbody>
<tr>
<td>Tmax (days)</td>
<td>0.45</td>
<td>2.45</td>
</tr>
<tr>
<td>T1/2 (days)</td>
<td>28.2</td>
<td>15.5</td>
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<tr>
<td>Cmax (µg/mL)</td>
<td>1.38 ± 0.05</td>
<td>1.48 ± 0.20</td>
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<tr>
<td>F (%)</td>
<td>81.22 ± 0.20</td>
<td>75.70 ± 2.66</td>
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<tr>
<td>Vss (mL/kg)†</td>
<td>59.26 ± 3.79</td>
<td>59.26 ± 3.79</td>
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<tr>
<td>Cl (mL/day/kg)</td>
<td>2.93 ± 0.61</td>
<td>2.93 ± 0.61</td>
</tr>
<tr>
<td>AUC0-inf (ng h/mL)</td>
<td>4.13 ± 10^5 (4.50 ± 10^5)</td>
<td>2.66 ± 10^5 (4.76 ± 10^5)</td>
</tr>
</tbody>
</table>

Results

- APG777 exhibited an average T1/2 of 27.6 days and Cl rate of 1.45 (mL/day/kg) in NHPs (Figure 3). Lebrikizumab exhibited an average T1/2 of 18.0 days and Cl rate of 2.93 (mL/day/kg) in NHPs (Figure 3).
- The Vss was observed to be 55.65 (mL/kg). APG777 was well-absorbed, with subcutaneous F determined to be 81.22% (Table 1).
- Lebrikizumab was well-absorbed, with subcutaneous F determined to be 75.70% (Table 1).

Conclusions

- APG777 demonstrated an increase in T1/2 and exposure and reduced clearance compared with a monoclonal antibody based on the published sequence of lebrikizumab. Both Cl and Vss of subcutaneous administration were dose-normalized using the subcutaneous bioavailability (F) indicated in the table; *F (%) was calculated by dividing the mean dose-normalized AUC0-inf following subcutaneous administration by the mean dose-normalized AUC0-inf following IV administration. AUC0-inf area under the serum concentration versus time curve from time 0 extrapolated to infinity. Cl, clearance; Cmax, maximum observed serum concentration; F, bioavailability; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous; SE, standard error; T1/2, half-life; Tmax, time to maximum observed serum concentration; Vss, volume of distribution at steady-state.

References


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