Figure 1. Pharmacokinetic profiles for KPL-404.

- Elimination was dose-dependent and consistent with target-mediated drug disposition (TMDD).
- Several cluster of differentiation (CD)40/CD40L-targeting agents are under clinical investigation in other diseases:
  - Non-human primate PK and receptor occupancy (RO) data informed the dosing regimen for the first-in-human study.
  - Suppression of ADA to KPL-404 is an independent indicator of target engagement and pharmacodynamic effect.

Table 1. Summary of Serum PK parameters of KPL-404.

<table>
<thead>
<tr>
<th>KPL-404</th>
<th>N=6</th>
<th>mg/kg</th>
<th>IV</th>
<th>SC</th>
<th>0.03 mg/kg</th>
<th>1 mg/kg</th>
<th>1*</th>
<th>3 mg/kg</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00, 3.05</td>
<td>1.00</td>
<td>1*</td>
<td>1.50</td>
<td>1.75</td>
<td>1.00</td>
</tr>
<tr>
<td>T1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>110.7, 203.0</td>
<td>16.2</td>
<td>1*</td>
<td>152</td>
<td>772</td>
<td>17.0</td>
</tr>
<tr>
<td>AUC0-inf</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19400, 96300</td>
<td>37.5</td>
<td>1*</td>
<td>2240</td>
<td>82.8b</td>
<td>35.5</td>
</tr>
</tbody>
</table>

In general, no consistent trends in serum KPL-404 PK were observed across the groups, and levels were consistent with expected pharmacokinetics for an IgG4 antibody in healthy volunteers.

Figure 2. Receptor Occupancy (RO) and T-cell Dependent Antibody Response (TDAR) to KLH antigen challenge.

- For participants receiving 1 or 5 mg/kg SC, full RO was observed through days 9, 29, and 57, respectively.
- For participants receiving 1 mg/kg SC, full RO was observed through days 9 and 29, respectively.
- The TDAR suppression observed with full RO in 1 mg/kg SC was maintained through day 29.

Table 2. Adverse Events reported by 20% of Healthy Participants Receiving KPL-404 IV, KPL-404 SC, and Placebo.

| Key Points | Extent and duration of full RO | Serum concentration dependence | KPL-404 suppressed TDAR (both primary and recall) when the receptor was fully occupied.

<table>
<thead>
<tr>
<th><strong>Anti-Drug Antibodies (ADA)</strong></th>
</tr>
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</table>
| In patients receiving IV KPL-404 administration, ADA were observed (at least one post-baseline time point) in 0/2 of 0.03 mg/kg, 5/6 at 0.3 mg/kg, 0/6 at 1 mg/kg, 2/6 at 3 mg/kg, and 0/6 at 10 mg/kg.
| In patients receiving SC KPL-404 administration, ADA were observed (at least one post-baseline time point) in 4/6 at 1 mg/kg, 5/6 at 5 mg/kg.
| In general, no consistent trends in serum KPL-404 PK: parameters (Cmax, AUC0-t) were observed due to ADA status, suggesting no impact of ADA status on PK of KPL-404 after IV or SC administration.
| ADA to KPL-404 were completely suppressed while concentrations of KPL-404 were above approximately 0.2 g/mL.
| ADA to KPL-404 were suppressed for at least 50 days at 0.3 mg/kg and at least 57 days at 10 mg/kg.

**METHODS**

Study Design and Participants

- Primary Endpoint
- Safety
- Secondary Endpoints
  - Pharmacokinetics (PK)
  - Immunochemical drug antibodies (ADAs)
  - Pharmacodynamics (PD)

Assessments
- Complete PK analysis in all patients following single IV or SC administration of KPL-404.
- CD40 RO was monitored in all cohorts except 0.03 mg/kg.
- Determined by flow cytometry-based assays performed on whole blood samples and measured as free CD40 on CD19-positive B cells. Binding of KPL-404 resulted in reduction of CD40 on B cells, and mean fluorescence intensity reduction of CD40 was measured and converted into Antibody Binding Capacity (ABC) using Quantum Simply Cellular™ (QSC) beads.
- KLH-induced primary immune response was monitored in cohorts receiving 1, 3, and 10 mg/kg IV and in cohorts receiving 1 and 5 mg/kg SC. KLH-induced secondary immune response was monitored in cohorts receiving 1, 3, and 5 mg/kg IV.
- Development of ADAs was monitored in all patients.

Safety
- Number of patients with treatment-emergent adverse events in each cohort vs (pos) IV and SC placebo groups from first day of dosing through day 60.
- Clinical laboratory tests, vital sign measurements, 12-lead ECGs, physical examination findings.

CONCLUSIONS

The pharmacokinetics of KPL-404 followed a TMDx model, with high dose cohorts showing slower elimination and longer duration of detectable concentrations with both IV and SC administration.

Full CD40 receptor occupancy was maintained through day 43 after single SC dose of 5 mg/kg and through at least 71 after a single IV dose of 10 mg/kg.

Pharmacodynamic assessments suggested full targeted engagement and dose-dependent suppression of TDAR for primary and secondary KLH challenge were achieved at pharmacologically relevant concentrations.

KPL-404 was well tolerated without serious adverse events, and safety data as well as findings in participants receiving KPL-404 versus participants receiving placebo.

The magnitude and duration of memory immune response suppression by KPL-404 support the further study of pharmacological chronic KPL-404 dosing regimens using both SC and IV administration.

The involvement of the CD40/C4D4 pathway in pathophysiology of multiple autoimmune diseases, including rheumatoid arthritis, Sjögren’s syndrome, Grav’s disease, and lupus supports further development of KPL-404 in a broad range of immune-mediated autoimmune diseases.

REFERENCES


DISCLOSURES

Dr. John Zilzer and Mary Boal reports travel/grant support from Alexion Pharma.