First-In-Human Study of KPL-716, Anti-Oncostatin M Receptor Beta Monoclonal Antibody, in Healthy Volunteers and Subjects With Atopic Dermatitis

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KPL-716 simultaneously inhibits both IL-31 and Oncostatin M (OSM) pruritic/inflammatory signaling

By binding a single epitope, KPL-716 simultaneously inhibits both IL-31 and OSM signaling, two pathways implicated in pruritus, inflammation, and fibrosis.
KPL-716 does not inhibit critical hematopoiesis signaling through OSM/LIFR

**IL-31 Signaling**
- Mast cell
- T_{h2} cells

**Type II OSM Signaling**
- Mφ
- T cells
- PMN
- Mast cell

**Type I OSM Signaling**
- Many cell types

**KPL-716**

**Pruritus**
- T_{h2} inflammation

**Fibrosis**
- Epidermal integrity
- T_{h2} inflammation

**Sensory Neurons**
- Keratinocytes
- Basophils
- Eosinophils
Atopic Dermatitis (AD) is a proxy for IL-31-driven pruritic diseases

**Role of IL-31 is well-established in pruritus and AD**

- IL-31 levels are elevated in AD and correlate with disease severity\(^1\)\(^-\)\(^3\)
- Keratinocytes and macrophages express IL-31R\(\alpha\), and circulating CLA\(^+\) T cells express IL-31 in AD\(^4\)
- Basophils release IL-31, and IL-31 increases IL-4 and IL-13 production in basophils; upregulation inhibited by anti-IL-31R\(\alpha\) and anti-OSMR\(\beta\)\(^5\)
- Anti-IL-31R\(\alpha\) treatment reduced pruritus in AD\(^6\)

**OSM plays an important role in T\(_h2\) inflammation, epidermal integrity, and fibrosis**

- Increases IL-4R\(\alpha\) and IL-13R\(\alpha\) production\(^8\)\(^-\)\(^13\)
- Increases IL-4 production; synergizes with IL-4 and IL-13 to increase eotaxin production in fibroblasts and airway smooth muscle cells\(^8\)\(^,\)\(^10\)\(^-\)\(^14\)
- Modulates genes important in keratinocyte activation and differentiation\(^8\)\(^,\)\(^9\)
- Levels are elevated in fibrotic diseases, and OSM over-expression in animal models results in fibrotic changes\(^11\)\(^,\)\(^15\)

KPL-716 Phase 1a/1b Study Design: Double-blind, placebo-controlled, single-ascending-dose

**Phase 1a:** Healthy volunteers (HV; n=50)

- Single IV Dose
- Single SC Dose

**Dose Groups**

- Single IV Dose
  - 1.5 mg/kg (6 active / 2 placebo)
  - 5 mg/kg (6 active / 2 placebo)
  - 10 mg/kg (6 active / 2 placebo)
  - 20 mg/kg (6 active / 2 placebo)

- Single SC Dose
  - 0.3 mg/kg SC (3 active / 2 placebo)
  - 1.5 mg/kg SC (6 active / 2 placebo)
  - 360 mg SC (7 active / 3 placebo)

**Primary endpoint (all subjects):**
- Safety and tolerability

**Secondary endpoint (all subjects):**
- PK and ADA

**Phase 1b:** Subjects with AD (n=32)

- Single IV Dose
  - 1.5 mg/kg (3 active / 2 placebo)
  - 7.5 mg/kg (10 active / 6 placebo)

- Single SC Dose
  - 1.5 mg/kg (4 active / 2 placebo)
  - Exploratory Efficacy analysis: KPL-716 7.5 mg/kg (n=10) vs. Placebo pooled (n=10)

**Dose Groups**

- 1.5 mg/kg (3 active / 2 placebo)

**Primary endpoint (all subjects):**
- Safety and tolerability

**Secondary endpoint (all subjects):**
- PK and ADA

AD = atopic dermatitis, IV = intravenous, SC = subcutaneous, PK = pharmacokinetics, ADA = anti-drug antibodies
Phase 1b: Washout Design, KPL-716 Monotherapy

Phase 1b: Subjects with AD (n=32)

Patient Experience

- Rescue for flares only
- TCS provided to use as needed
- d0
- d28
- d60
- d90
- d120
- d-7
- SV1
- SV2
- d-7
- d0
- d28
- d60
- d90
- d120
- SV1
- SV2

Entry Criteria:
- IGA of 3 or 4
- ≥10% BSA
- WI-NRS ≥ 7 SV1
- WI-NRS > 5 d-1

PK & safety monitoring

Immunogenicity

- Topical corticosteroids prohibited
- TCI, Phosphodiesterase inhibitors, anti-histamines prohibited
- Daily e-diary worst itch WI-NRS (past 24 hours)
- EASI, IGA, SCORAD at SV1, SV2, day -1 and days 4, 7, 14, 21, 28, and 60

Primary endpoint:
- Safety and tolerability

Secondary endpoint:
- PK and ADA

Exploratory endpoints:
- Target engagement
- Early Signal of Efficacy

- Systemic corticosteroids, immunosuppressants, immunomodulators, and phototherapy were prohibited from 4 weeks or 5 half-lives before SV2 until d60
- Topical calcineurin inhibitors (TCI), topical phosphodiesterase inhibitors, and anti-histamines were prohibited from d-7 until d60
- Topical corticosteroids (TCS) were prohibited from d-7 until d28

AD = atopic dermatitis, IV = intravenous, SC = subcutaneous, PK = pharmacokinetics, ADA = anti-drug antibodies, IGA = Investigator’s Global Assessment (severity scale), WI-NRS = Worst Itch Numerical Rating Scale, BSA = Body Surface Area, EASI = Eczema Area and Severity Index, SCORAD = Scoring atopic dermatitis (severity scale), SV1 = Screening Visit #1, SV2 = Screening Visit #2
Baseline Parameters were Balanced

<table>
<thead>
<tr>
<th>Baseline demographics/disease characteristics: AD</th>
<th>KPL-716</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.5 mg/kg IV</td>
<td>Pooled IV</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>29.7 (11.2)</td>
<td>41.7 (10.9)</td>
</tr>
<tr>
<td>Male, %</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>White, %</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Elevated IgE, %</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>History of any allergic disease, %</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>#AD flares in past year, mean (SD)</td>
<td>28.1 (41.6)</td>
<td>3.7 (3.5)</td>
</tr>
<tr>
<td>Body surface area affected by AD, mean (SD)</td>
<td>24.2 (8.0)</td>
<td>34.1 (28.0)</td>
</tr>
<tr>
<td>Weekly average WI-NRS, mean (SD)</td>
<td>8.0 (1.3)</td>
<td>8.2 (0.7)</td>
</tr>
<tr>
<td>Total EASI, mean (SD)</td>
<td>19.9 (7.6)</td>
<td>25.3 (14.1)</td>
</tr>
<tr>
<td>Total SCORAD, mean (SD)</td>
<td>66.7 (10.7)</td>
<td>60.7 (13.7)</td>
</tr>
<tr>
<td>IGA=3, %</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>IGA=4, %</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Baseline is defined as the last measurement prior to dosing.

AD = atopic dermatitis, IV = intravenous, IGA = Investigator’s Global Assessment (severity scale), WI-NRS = Worst Itch Numerical Rating Scale, EASI = Eczema Area and Severity Index, SCORAD = Scoring atopic dermatitis (severity scale)
KPL-716 was Well-Tolerated

- No Deaths
- No SAEs
- No Discontinuations due to AEs
- No Infusion Reactions
- No Injection Site Reactions

- No Thrombocytopenia
- No Peripheral Edema
- No Conjunctivitis

- Drug-Related Treatment Emergent Adverse Events (DR-TEAEs) infrequent and not related to dose

<table>
<thead>
<tr>
<th>Healthy volunteers</th>
<th>KPL-716 (IV)</th>
<th>Placebo (IV)</th>
<th>KPL-716 (SC)</th>
<th>Placebo (SC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE</strong></td>
<td>1.5 mg/kg n=6</td>
<td>5 mg/kg n=6</td>
<td>10 mg/kg n=6</td>
<td>20 mg/kg n=6</td>
</tr>
<tr>
<td>DR-TEAE</td>
<td>0</td>
<td>Mild headache (1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with atopic dermatitis</th>
<th>KPL-716 (IV)</th>
<th>Placebo (IV)</th>
<th>KPL-716 (SC)</th>
<th>Placebo (SC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE</strong></td>
<td>0.3 mg/kg n=3</td>
<td>1.5 mg/kg n=3</td>
<td>7.5 mg/kg n=10</td>
<td>Pooled n=10</td>
</tr>
<tr>
<td>DR-TEAE</td>
<td>0</td>
<td>Mild headache (1), Decreased appetite (1)</td>
<td>Moderate dizziness (1)</td>
<td>Mild somnolence (1)</td>
</tr>
<tr>
<td>AD flare</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Study day of AD flare</td>
<td>7</td>
<td>N/A</td>
<td>14, 20</td>
<td>1, 5, 45</td>
</tr>
</tbody>
</table>

†The only moderate DR-TEAE occurred after a protocol violation.
KPL-716 demonstrated dose-dependent elimination (TMDD)
Exploratory Efficacy Endpoints and Analysis Plan

Efficacy Analysis:

• 10 KPL-716 subjects (7.5 mg/kg IV) versus 10 placebo subjects (pooled IV) from baseline to Day 28

• “Last Observation Carried Forward” approach used for data values after rescue medication administered. Subject was considered non-responder after rescue (responder analysis).
  – Two KPL-716: 2 AD flares (d15 and d21)
  – Three placebo: 2 AD flares (d3, d14), 1 anti-histamine use for upper respiratory infection (d26)

• Similar results obtained if data values after rescue medication administration were included or excluded

Efficacy Endpoints:

• Pruritus:
  – Weekly average of daily WI-NRS (worst itch in past 24 hours) collected by daily eDiary
  – Pruritus Visual Analog Scale, a component of SCORAD (average itch in past 3 days) collected at study visits

• Sleep loss VAS:
  – A component of SCORAD (average sleep loss in past 3 nights)

• Eczema Area Severity Index (EASI)

AD = atopic dermatitis, IV = intravenous, WI-NRS = Worst Itch Numerical Rating Scale, EASI = Eczema Area and Severity Index, SCORAD = Scoring atopic dermatitis (severity scale)
KPL-716 (single dose) reduced pruritus versus Placebo
(28 day monotherapy period)

**Pruritus Visual Analog Scale (VAS)**

**Weekly Average of “Worst Itch Numerical Rating Scale” (WI-NRS)**

In subjects who received rescue medication, last observation was carried forward. Two KPL-716 recipients (d15, d21) and three placebo recipients (d3, d14, d26).

*SCORAD = Scoring atopic dermatitis (severity scale)*
KPL-716 (single dose) reduced WI-NRS by ≥4 Points versus Placebo (28 day monotherapy period)

Subject was considered non-responder after rescue. Two KPL-716 recipients (d15, d 21) and three placebo recipients (d3, d14, d26).

WI-NRS = Worst Itch Numerical Rating Scale
KPL-716 (single dose) reduced WI-NRS to a greater magnitude versus Placebo (28 day monotherapy period)

KPL-716 (7.5mg/kg IV)

Placebo (Pooled IV)

Subject was considered non-responder after rescue. Two KPL-716 recipients (d15, d21) and three placebo recipients (d3, d14, d26).
KPL-716 (single dose) reduced Sleep Loss, an important QoL parameter, versus Placebo (28 day monotherapy period)

Sleep Loss VAS*

* A component of SCORAD.

In subjects who received rescue medication, last observation was carried forward. Two KPL-716 recipients (d15, d 21) and three placebo recipients (d3, d14, d26).

QoL = Quality of Life, VAS = Visual Analog Scale, SCORAD = Scoring atopic dermatitis (severity scale)
KPL-716 (single dose) reduced Atopic Dermatitis Disease Severity versus Placebo
(28 day monotherapy period)

Eczema Area and Severity Index (EASI)

In subjects who received rescue medication, last observation was carried forward. Two KPL-716 recipients (d15, d21) and three placebo recipients (d3, d14, d26).
Summary

• First-in-Human, double-blind, placebo-controlled study of KPL-716 met the primary endpoint:
  – KPL-716 was well-tolerated in both healthy volunteers and subjects with AD

• KPL-716 engaged its target and demonstrated an Early Signal of Efficacy with pruritus reduction
  – Reduction in disease severity (EASI) and sleep loss were also demonstrated
  – Repeated-Single-Dose study in subjects with AD is ongoing; longer duration will provide additional efficacy data

• Data support further development of KPL-716 in chronic pruritic diseases
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