Safety, Tolerability and Anti-Pruritic Effect of KPL-716, Anti-Oncostatin M Receptor Beta Monoclonal Antibody, from a Phase 1a/1b Clinical Trial in Healthy Volunteers and Participants with Atopic Dermatitis

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BACKGROUND

KPL-716

- KPL-716 is an anti-oncostatin M receptor beta monoclonal antibody being investigated by Kiniksa Pharmaceuticals, Ltd. as a potential treatment for chronic pruritic diseases
- KPL-716 simultaneously inhibits both IL-31 and OSM signaling by binding a single epitope, yet does not inhibit critical hematopoiesis signaling through oncostatin M/leukemia inhibitory factor (LIF) (**Figure 1**)

Figure 1: KPL-716 impact on IL-31 and OSM signaling

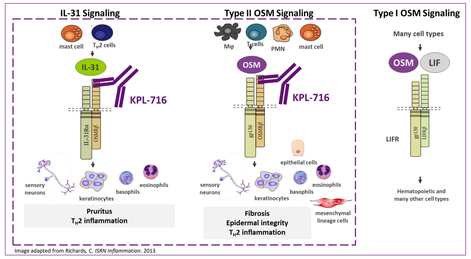


Image adapted from Richards, C. ISRN Inflammation. 2013

IL-31 and Oncostatin M (OSM) Signaling: Atopic Dermatitis (AD) as a proxy for pruritic diseases

- IL-31 and Oncostatin M (OSM) signaling are implicated in pruritus, inflammation, and fibrosis (**Table 1**)
- Inhibition of IL-31 and OSM is a potential therapeutic strategy in chronic pruritic diseases

Table 1: Role of IL-31 and OSM

IL-31, an inflammatory cytokine and known pruritogen, has a well-established role in pruritic conditions, including AD	OSM plays an important role in T_H2 inflammation, epidermal integrity, and fibrosis
• IL-31 levels are elevated in AD and correlate with disease severity[1-3] • Keratinocytes and macrophages express IL-31Rα, 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-31Rα and anti-OSMRβ[5] • Anti-IL-31Rα treatment reduces pruritus in AD[6]	• Increases IL-4Rα and IL-13Rα 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]

METHODS

Study Design

- Double-blind, randomized, placebo-controlled, single-ascending dose study (**Figure 2, 3**)

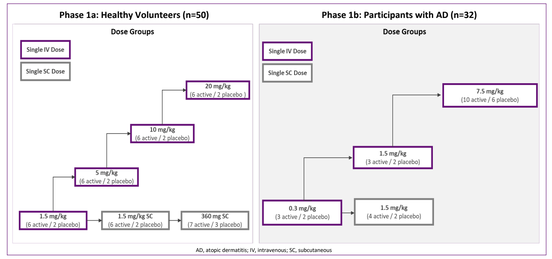
Objectives

- To evaluate safety, tolerability, pharmacokinetics (PK), and immunogenicity in healthy volunteers (Phase 1a) and participants with atopic dermatitis (Phase 1b)

Endpoints

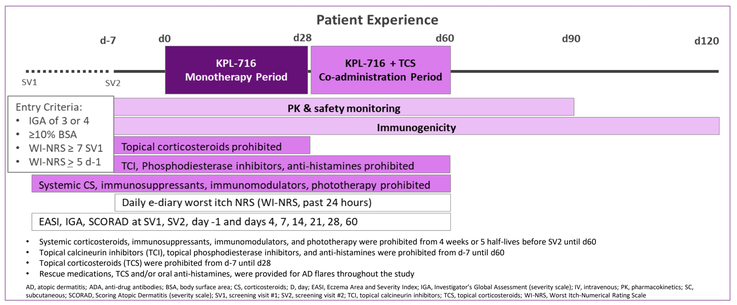
- Primary: Safety and tolerability
- Secondary: PK and anti-drug antibodies (ADA)

Figure 2: Phase 1a/1b Study Design



AD, atopic dermatitis; IV, intravenous; SC, subcutaneous

Figure 3: Phase 1b Washout Design, KPL-716 Sequential Monotherapy Followed by Coadministration Paradigm in AD



- 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
- Rescue medications, TCS and/or oral anti-histamines, were provided for AD flares throughout the study

AD, atopic dermatitis; ADA, anti-drug antibodies; BSA, body surface area; CS, corticosteroids; D, day; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment (severity scale); IV, intravenous; PK, pharmacokinetics; SC, subcutaneous; SCORAD, Scoring Atopic Dermatitis (severity scale); SV1, screening visit #1; SV2, screening visit #2; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; WI-NRS, Worst Itch-Numerical Rating Scale

Methods (continued)

Phase 1b Exploratory Efficacy Analysis

- KPL-716 7.5 mg/kg IV versus placebo (pooled IV) from baseline to Day 28
- 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)
- "Last Observation Carried Forward" approach used for data values after rescue medication administered; participant was considered non-responder after rescue (responder analysis)

Results

Baseline Demographics

- Baseline demographics in the Phase 1b exploratory analysis group were balanced (**Table 2**)

Safety

- Single-dose KPL-716 was well-tolerated in healthy volunteers (**Table 3**) and participants with AD (**Table 4**)
  - No deaths, serious adverse events (SAE) or discontinuations due to AEs
  - No infusion reactions or injection site reactions
  - No thrombocytopenia, peripheral edema or conjunctivitis
  - Drug-related treatment emergent AEs (DR-TEAE) infrequent and not related to dose

Table 2: Phase 1b Baseline Demographics/Disease Characteristics in AD

Demographics/disease characteristics:	KPL-716 7.5 mg/kg IV (n=10)	Placebo Pooled IV (n=10)
Age, mean (SD), years	29.7 (11.2)	41.7 (10.9)
Male, %	50	70
White, %	70	70
Elevated IgE, %	60	60
History of any allergic disease, %	40	60
#AD flares in past year, mean (SD)	28.1 (41.6)	3.7 (3.5)
Body surface area affected by AD, mean (SD)	24.2 (8.0)	34.1 (28.0)
Weekly average WI-NRS, mean (SD)	8.0 (1.3)	8.2 (0.7)
Total EASI, mean (SD)	19.9 (7.6)	25.3 (14.1)
Total SCORAD, mean (SD)	66.7 (10.7)	56.2 (12.7)
IGA 3 / IGA 4, %	80 / 20	80 / 20

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)

Table 3: Phase 1a Study Safety of KPL-716 in Healthy volunteers

Adverse Event	KPL-716 (IV) 1.5 mg/kg n=6	5 mg/kg n=6	10 mg/kg n=6	20 mg/kg n=6	Placebo (IV) Pooled n=8	KPL-716 (SC) 1.5 mg/kg n=6	360 mg n=7	Placebo (SC) Pooled n=5
DR-TEAE	0	Mild headache (1)	0	0	0	Mild flushing (1)	Mild anemia (1)	0

Table 4: Phase 1b Study Safety of KPL-716 in Participants with Atopic Dermatitis

Adverse Event	KPL-716 (IV) 0.3 mg/kg n=3	1.5 mg/kg n=3	7.5 mg/kg n=10	Placebo (SC) Pooled n=10	KPL-716 (SC) 1.5 mg/kg n=4	Placebo (SC) Pooled n=2
DR-TEAE	0	Mild headache (1), Decreased appetite (1)	Moderate dizziness (1)	Mild somnolence (1)	Mild dizziness (1)	0
AD flare	1	0	2	3	0	0
Study day of AD flare	7	N/A	14, 20	1, 5, 45	N/A	N/A

AD, atopic dermatitis; DR-TEAE, drug-related treatment emergent adverse events; IV, intravenous; SC, subcutaneous
Data in ( ) correspond to the number of events for each term

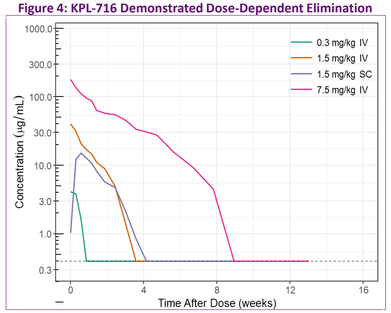
Pharmacokinetics

- KPL-716 demonstrated dose dependent elimination, target-mediated drug disposition (TMDD; **Figure 4**)

Phase 1b Exploratory Efficacy

- Responder Analysis:
  - KPL-716 (n=2): 2 AD flares (rescue on d15 and d21)
  - Placebo (n=3): 2 AD flares (rescue on d3 and d14), 1 anti-histamine use for URI (rescue on d26)
  - Similar results obtained if data values after rescue medication administration were included or excluded
- Compared to placebo, single-dose KPL-716 reduced pruritus (**Figure 5a**); WI-NRS by ≥4 points (**Figure 5b**) and to a greater magnitude (**Figure 5c**); sleep Loss (**Figure 5d**); AD disease severity (**Figure 5e**)

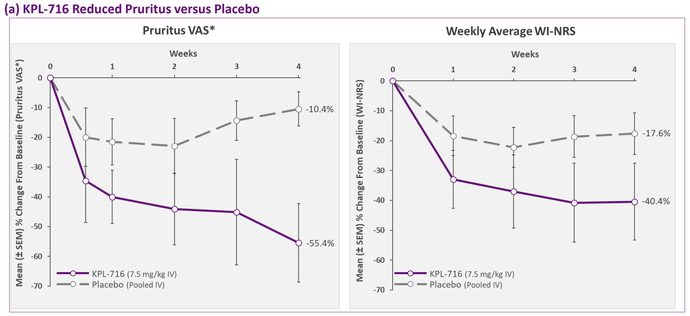
Figure 4: KPL-716 Demonstrated Dose-Dependent Elimination



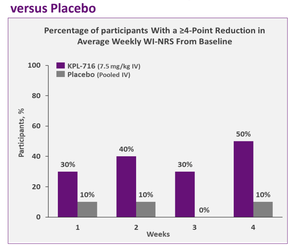
Results (continued)

Figure 5: Phase 1b Exploratory Efficacy of single dose KPL-716 vs Placebo (28 day monotherapy period)

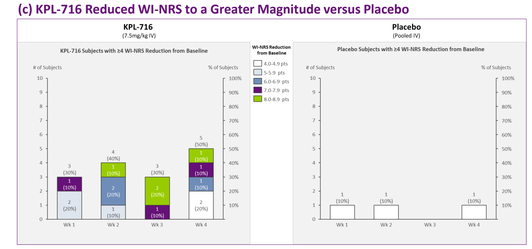
(a) KPL-716 Reduced Pruritus versus Placebo



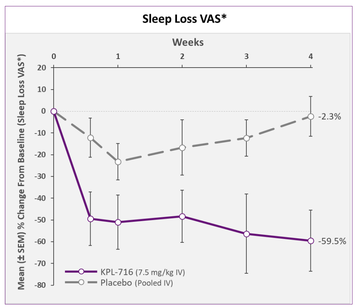
(b) KPL-716 Reduced WI-NRS by ≥4 Points versus Placebo



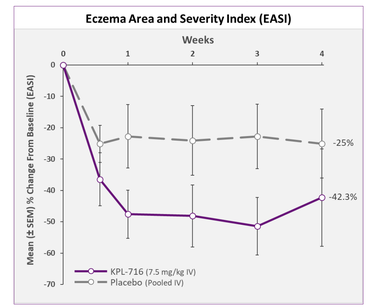
(c) KPL-716 Reduced WI-NRS to a Greater Magnitude versus Placebo



(d) KPL-716 Reduced Sleep Loss versus Placebo



(e) KPL-716 Reduced AD Disease Severity versus Placebo



*A component of scoring atopic dermatitis (SCORAD, severity scale); WI-NRS, Worst Itch Numerical Rating Scale; VAS, Visual analog scale
In participants who received rescue medication, last observation was carried forward: KPL-716 recipients (n=2; d15, d 21) and placebo recipients (n=3; d3, d14, d26)

CONCLUSIONS

- 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
  - Reductions in disease severity (EASI) and sleep loss were also demonstrated
  - Repeated-Single-Dose study in subjects with AD has completed enrollment; continued follow-up will provide additional safety and efficacy data
- Data support further development of KPL-716 in chronic pruritic diseases

DISCLOSURES:
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