KPL-716, Anti-oncostatin M Receptor Beta Antibody, Reduced Pruritus in Atopic Dermatitis

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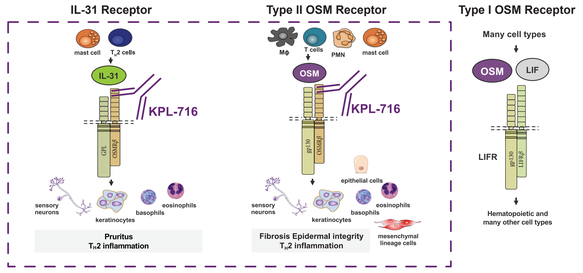
BACKGROUND

KPL-716

- KPL-716 is a fully human monoclonal antibody against oncostatin M receptor β (OSMRβ). KPL-716 is being investigated by Kiniksa Pharmaceuticals, Ltd. as a potential treatment for chronic pruritic diseases
- By binding a single epitope, KPL-716 simultaneously inhibits both interleukin (IL)-31 and oncostatin M (OSM) signaling, 2 pathways implicated in pruritus, inflammation, hyperkeratosis, and fibrosis. KPL-716 does not inhibit signaling of OSM via the leukemia inhibitory factor (LIF) receptor, a pathway important in hematopoiesis and platelet synthesis (**Figure 1**)

Figure 1. KPL-716 Impact on IL-31 and OSM Signaling



IL = interleukin, LIF, leukemia inhibitory factor, OSM = oncostatin M, T$_h$2 = type 2 T helper cell. Image adapted from Richards C. *ISRN Inflammation*. 2013;2013:1-23.[1]

Atopic dermatitis (AD) as a proxy for IL-31–driven pruritic diseases

- Inhibition of IL-31 and OSM is a potential therapeutic strategy in chronic pruritic diseases

Role of IL-31 and OSM in AD

Role of IL-31 is well established in pruritus and AD	OSM plays an important role in type 2 T helper cell (T$_h$2) inflammation, epidermal integrity, and fibrosis
• Levels are elevated in AD and correlate with disease severity[2-4] • Keratinocytes and macrophages express IL-31Rα, and circulating CLA$^+$ T cells express IL-31 in AD[5] • Basophils release IL-31, and IL-31 increases IL-4 and IL-13 production in basophils; upregulation is inhibited by anti-IL-31Rα and anti-OSMRβ[6] • Anti-IL-31Rα treatment reduced pruritus in AD[7,8]	• Increases IL-4 receptor α (IL-4 Rα) and IL-13Rα production[9-14] • Increases IL-4 production; synergizes with IL-4 and IL-13 to increase eotaxin production in fibroblasts and airway smooth muscle cells[9,11-15] • Modulates genes important in keratinocyte activation and differentiation[9,10] • Levels are elevated in fibrotic diseases, and OSM over-expression in animal models results in fibrotic changes[12,16]

METHODS

Study Design

- Randomized, double-blind, placebo (PBO)-controlled, single-dose study

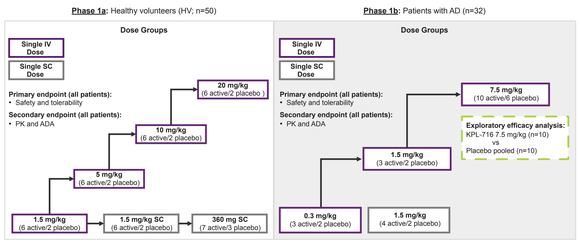
Objective

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

Endpoints

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

Figure 2. KPL-716 Phase 1a/1b Study Design: Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose

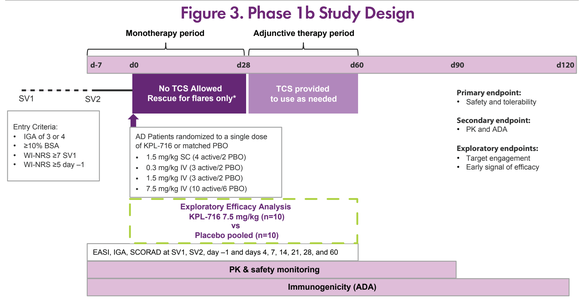


AD = atopic dermatitis, ADA = anti-drug antibodies, IV = intravenous, PK = pharmacokinetics, SC = subcutaneous.

Exploratory Efficacy Analysis

- Intravenous (IV) KPL-716 7.5 mg/kg (n=10) vs PBO pooled (n=10)
- The study consisted of 2 phases: KPL-716 monotherapy period (day −7 to 28), when other AD medications were prohibited, and adjunctive therapy period (>day 28), when patients used topical corticosteroids (TCS) as needed
- Clinical data included weekly average of daily e-diary Worst Itch Numeric Rating Scale (WI-NRS) as well as periodic pruritus and sleep-loss visual analogue scale (VAS) and Eczema Area and Severity Index (EASI) assessments until day 60
- Observation that a single dose of IV KPL-716 7.5 mg/kg provided serum levels >5 µg/mL through 44 days post-dose in 89% of patients with available PK measurements prompted us to explore KPL-716 efficacy beyond the monotherapy period. This report provides data through day 60
  - Using the as-observed dataset, WI-NRS, pruritus VAS, sleep-loss VAS, and EASI were compared in 20 patients randomized to receive KPL-716 7.5 mg/kg IV (n=10) or PBO (n=10)

Figure 3. Phase 1b Study Design



AD = atopic dermatitis, ADA = anti-drug antibodies, BSA = body surface area, EASI = Eczema Area and Severity Index, IGA = Investigator's Global Assessment (severity scale), IV = intravenous, PBO = placebo, PK = pharmacokinetics, SC = subcutaneous, SCORAD = Scoring Atopic Dermatitis severity scale, SV1 = screening visit #1, SV2 = screening visit #2, TCS = topical corticosteroids, WI-NRS = Worst Itch Numerical Rating Scale.*Systemic corticosteroids, immunosuppressants, immunomodulators, and phototherapy were prohibited from 4 weeks (for oral treatments and phototherapy) or 5 half-lives (for other routes of administration) before SV2 until day 60. Topical calcineurin inhibitors (TCI), topical phosphodiesterase inhibitors, and antihistamines were prohibited from day −7 until day 60. TCS were prohibited from day −7 until day 28.

Efficacy analysis

- 20 patients were randomized to receive KPL-716 (10 patients, 7.5 mg/kg IV) or PBO (10 patients, pooled IV)
- An "as-observed" approach was used for this analysis vs the prior analysis presented at the European Academy of Dermatology and Venerology (EADV) Congress in September 2018, which used "last observation carried forward"[17]
  - This analysis includes data from patients post-rescue: in the KPL-716 monotherapy period,
    - KPL-716 group (n=2): 2 AD flares (day 15, day 21)
    - PBO group (n=3): 2 AD flares (day 3, day 14), 1 antihistamine use for upper respiratory infection (day 26)

Efficacy endpoints

- Pruritus
  - Weekly average of daily WI-NRS (worst itch in past 24 hours) collected by daily e-diary
  - Pruritus VAS, a component of Scoring Atopic Dermatitis (SCORAD) severity scale (average itch in past 3 days), collected at study visits
- Sleep loss: a component of SCORAD (average sleep loss in past 3 nights)
- EASI was used to grade the extent of eczema as well as severity of signs and symptoms

RESULTS

Patients

- Baseline parameters were generally balanced between treatment groups (**Table 1**)
- The number of AD flares in the past year was substantially higher for the KPL-716 treatment group compared with PBO

Table 1. Baseline[a] Demographics and Disease Characteristics

Demographic/Disease Characteristic	KPL-716 7.5 mg/kg IV	Placebo Pooled IV
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

AD = atopic dermatitis, EASI = Eczema Area and Severity Index, IGA = Investigator's Global Assessment (severity scale), IV = intravenous, SCORAD = Scoring Atopic Dermatitis severity scale, WI-NRS = Worst Itch Numerical Rating Scale. [a]Baseline is defined as the last measurement prior to dosing.

Safety and Tolerability

- Single-dose KPL-716 was well tolerated in healthy volunteers (phase 1a; **Table 2**) and participants with AD (phase 1b; **Table 3**)
  - No deaths or serious adverse events occurred, and there were no discontinuations due to adverse events
  - No infusion reactions or injection site reactions occurred
  - No cases of thrombocytopenia, peripheral edema, or conjunctivitis occurred
  - Drug-related treatment-emergent adverse events were infrequent and not related to dose

Table 2. Phase 1a Study Safety of KPL-716 in Healthy Volunteers

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

Data in parentheses correspond to the number of events for each term. DR-TEAE, drug-related treatment-emergent adverse events, IV, intravenous, SC, subcutaneous.

Table 3. Phase 1b Study Safety of KPL-716 in Participants With Atopic Dermatitis

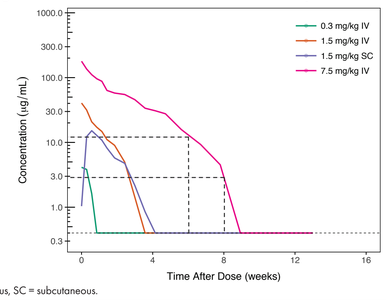
	KPL-716 (IV)			Placebo (IV)	KPL-716 (SC)	Placebo (SC)
Adverse Event	0.3 mg/kg n=3	1.5 mg/kg n=3	7.5 mg/kg n=10	Pooled n=10	1.5 mg/kg n=4	Pooled n=2
DR-TEAE	0	Mild headache (n=1), decreased appetite (n=1)	Moderate dizziness (n=1)	Mild somnolence (n=1)	Mild dizziness (n=1)	0
AD flare	1	0	2	3	0	0
Study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

Data in parentheses correspond to the number of events for each term. Green line indicates groups compared in efficacy analysis below. AD, atopic dermatitis, DR-TEAE, drug-related treatment-emergent adverse events, IV, intravenous, SC, subcutaneous.

Pharmacokinetics

- KPL-716 demonstrated target-mediated drug disposition (**Figure 4**)

Figure 4. KPL-716 Demonstrated Dose-Dependent Elimination

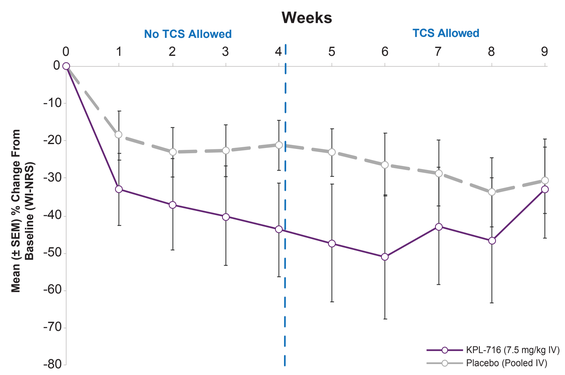


IV = intravenous, SC = subcutaneous.

Efficacy

- A single IV dose of KPL-716 7.5 mg/kg reduced pruritus compared with placebo
  - KPL-716 recipients experienced a greater WI-NRS improvement compared with PBO recipients. The improvement in WI-NRS began as early as week 1 (−33% vs −18.5%), increased throughout the monotherapy period (week 4, −43.8% vs −21.2%), and persisted in the adjunctive period with coadministration of TCS (week 6, −51.1% vs −26.3%) (**Figure 5**)

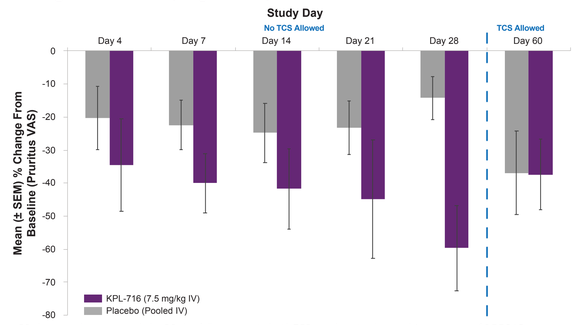
Figure 5. KPL-716 (Single Dose[a]) Reduced Pruritus Worst Itch Versus Placebo[b]



[a]28-day monotherapy period plus 30-day follow-up period with TCS as adjunctive therapy. [b]As-observed analysis. Data were not censured after use of rescue. In the monotherapy period: 2 patients receiving KPL-716 (D15 and D21); 3 patients receiving placebo (D3, D14, D26). WI-NRS collected daily by e-diary. Weekly Average WI-NRS: calculated from week 1 to week 9. IV = intravenous, TCS = topical corticosteroids, WI-NRS = Worst Itch Numerical Rating Scale.

- KPL-716 recipients also experienced a greater improvement in pruritus VAS compared with PBO during the monotherapy period when these assessments were performed periodically. The effect on pruritus VAS matched that of PBO by the end of the adjunctive period (**Figure 6**)

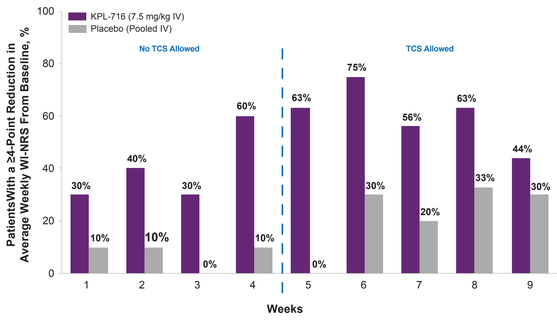
Figure 6. KPL-716 (Single Dose[a]) Reduced Pruritus VAS Versus Placebo[b,c]



[a]28-day monotherapy period plus 30-day follow-up period with TCS as adjunctive therapy. [b]A component of SCORAD. [c]As-observed analysis. Data were not censured after use of rescue. In the monotherapy period: 2 patients receiving KPL-716 (D15 and D21); 3 patients receiving placebo (D3, D14, D26). VAS was collected at study visits on days 4, 7, 14, 21, 28, and 60. VAS was not collected between day 28 and day 60. IV = intravenous, SCORAD = Scoring Atopic Dermatitis severity scale, TCS = topical corticosteroids, VAS = visual analogue scale.

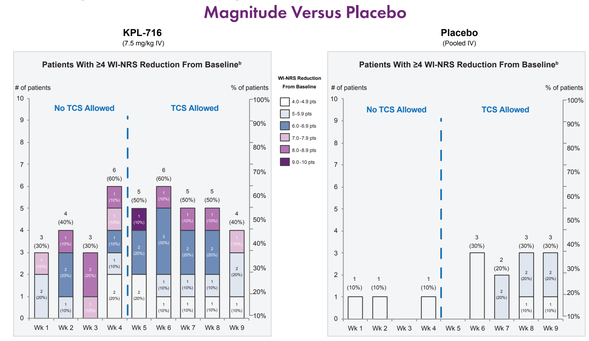
- A higher percentage of KPL-716 recipients demonstrated a ≥4-point decrease in WI-NRS compared with PBO recipients. The ≥4-point responder difference appeared as early as week 1 (30% vs 10%), increased throughout the monotherapy period (60% vs 10%), and persisted in the adjunctive period with coadministration of TCS (week 6: 75% vs 30%) (**Figure 7**)

Figure 7. KPL-716 (Single Dose[a]) Reduced WI-NRS by ≥4 Points Versus Placebo[b]



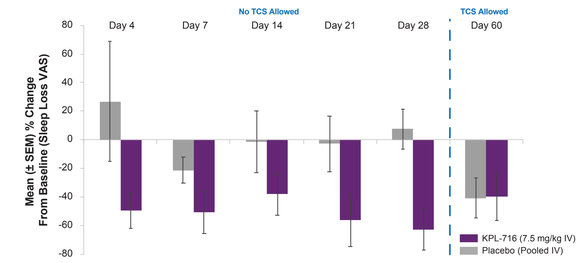
[a]28-day monotherapy period plus 30-day follow-up period with TCS as adjunctive therapy. [b]As-observed analysis. Data were not censured after use of rescue. In the monotherapy period: 2 patients receiving KPL-716 (D15 and D21); 3 patients receiving placebo (D3, D14, D26). Denominator includes all patients with non-missing data. IV = intravenous, TCS = topical corticosteroids, WI-NRS = Worst Itch Numerical Rating Scale.

Figure 8. KPL-716 (Single Dose[a]) Reduced WI-NRS to a Greater Magnitude Versus Placebo



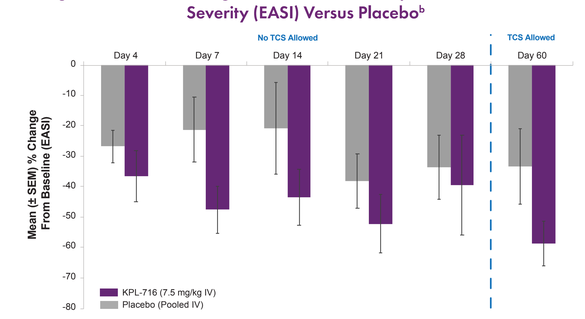
[a]28-day monotherapy period plus 30-day follow-up period with TCS as adjunctive therapy. [b]As-observed analysis. Data were not censured after use of rescue. In the monotherapy period: 2 patients receiving KPL-716 (D15 and D21); 3 patients receiving placebo (D3, D14, D26). Denominator includes all patients. IV = intravenous, TCS = topical corticosteroids, WI-NRS = Worst Itch Numerical Rating Scale.

Figure 9. KPL-716 (Single Dose[a]) Reduced Sleep Loss, an Important QoL Parameter, Versus Placebo[b,c]



[a]28-day monotherapy period plus 30-day follow-up period with TCS as adjunctive therapy. [b]A component of SCORAD. [c]As-observed analysis. Data were not censured after use of rescue. In the monotherapy period: 2 patients receiving KPL-716 (D15 and D21); 3 patients receiving placebo (D3, D14, D26). VAS was collected at study visits on days 4, 7, 14, 21, 28, and 60. VAS was not collected between days 28 and 60. QoL = quality of life, SCORAD = Scoring Atopic Dermatitis (severity scale), TCS = topical corticosteroids, VAS = visual analogue scale.

Figure 10. KPL-716 (Single Dose[a]) Reduced Atopic Dermatitis Disease Severity (EASI) Versus Placebo[b]



[a]28-day monotherapy period plus 30-day follow-up period with TCS as adjunctive therapy. [b]As-observed analysis. Data were not censured after use of rescue. In the monotherapy period: 2 patients receiving KPL-716 (D15 and D21); 3 patients receiving placebo (D3, D14, D26). EASI was collected at study visits on days 4, 7, 14, 21, 28, and 60. EASI was not collected between days 28 and 60. IV = intravenous, TCS = topical corticosteroids, VAS = visual analogue scale.

CONCLUSIONS

- This first-in-human, double-blind, placebo-controlled study of KPL-716 met its primary endpoint
  - KPL-716 was well tolerated in both healthy volunteers and patients with AD
- KPL-716 remained detectable in the serum for 8 weeks after a single 7.5-mg/kg IV dose, and levels were above 5 µg/mL through 44 days post-dose in 89% of patients with available PK measurements
- KPL-716 engaged its target and demonstrated an early signal of efficacy with pruritus reduction
  - Improvement in pruritus began as early as 1 week post-dose, increased throughout the monotherapy period, and persisted in the adjunctive period with coadministration of TCS
  - Reductions in sleep loss and disease severity (EASI) were also demonstrated
- These data confirm and extend the previously reported findings demonstrating the anti-pruritic effect of OSMRβ inhibition, supporting further development of KPL-716 in chronic pruritic indications
- A repeated-single-dose study in 40 patients with AD has completed enrollment; the longer treatment duration and follow-up will provide additional safety and efficacy data on both pruritus and disease severity

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DISCLOSURES

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