KPL-716, Anti-oncostatin M Receptor Beta Antibody, Reduced Pruritus in Atopic Dermatitis
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BACKGROUND
KPL-716
- Is a fully human monoclonal antibody against oncostatin M receptor (c-OSMR)
- 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 flares. KPL-716 does not inhibit signaling of OSM via the laminin inhibitory factor (LIF) receptors, a pathway important in hematopoietic and skeletal stem cell biology.

Atopic dermatitis (AD) as a proxy for IL-31-driven pruritic diseases
- Inhibition of IL-31 and OSM in a potential therapeutic strategy in chronic pruritic diseases

Role of IL-31 in AD
- Levels are elevated in AD and correlate with disease severity.
- Keratinocytes and macrophages express IL-31, and circulating IL-31 is elevated in AD.
- IL-31 increases levels of pro-inflammatory cytokines and chemokines, including IL-17 and TNF-alpha
- Levels are elevated in AD, keratinocytes, and small and medium-sized arteries.
- Anti-IL-31 treatment reduced pruritus in AD.

Role of OSM in AD
- Levels are elevated in AD and correlate with disease severity.
- OSM increases expression of pro-inflammatory cytokines and chemokines, including IL-17 and TNF-alpha.
- Levels are elevated in AD, keratinocytes, and small and medium-sized arteries.
- Anti-OSM treatment reduced pruritus in AD.

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 (ADAs)

RESULTS
Patients
- Baseline parameters were generally balanced between treatment groups (Table 1)

Safety and Tolerability
- Single-dose KPL-716 was well tolerated in healthy volunteers (phase 1a) and participants with AD (phase 1b)
- No deaths or serious adverse events occurred, and there were no discontinuations due to adverse events.
- No infusion reactions or intolerable 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

CONCLUSIONS
- This first-in-human, double-blind, placebo-controlled single-dose study of KPL-716 met its primary endpoint.
- KPL-716 was well tolerated in both healthy volunteers and patients with AD.
- KPL-716 reduced pruritus in the skin for 6 weeks after a single 7.5-mg/kg IV dose, and ADAs were below 5.0 µg/mL.
- KPL-716 engaged its target and demonstrated an early signal of efficacy with pruritus reduction.

EXPLORATORY EFFICACY ANALYSIS
- Interim analyses (12 weeks) of KPL-716 vs PBO will be presented.
- The study consisted of 2 phases: KPL-716 microtherapy period (day 7 to 28), when other AD medications were prohibited, and withdrawal therapy period (day 29), when patients used topical corticosteroids (TCS) as needed.
- Clinical data included weekly accumulation of daily pruritus Intensity Visual Analog Scale (VISA) and Eczema Area and Severity Index (EASI) assessments by day 28.
- Observation: a single dose of KPL-716 7.5 mg/kg provided superior levels of 5.9 µg/mL on day 28 in 51% of patients with available PK measurements as compared to placebo (PBO) on day 28.

EXPLORATORY EFFICACY ANALYSIS
- Eczema Area and Severity Index (EASI) assessments until day 60
- Volunteers (phase 1a) and participants with AD (phase 1b)
- Phase 1a Study Safety of KPL-716 in Healthy Volunteers

EXPLORATORY EFFICACY ANALYSIS
- KPL-716 demonstrated target-mediated drug disposition (Figure 4)

EXPLORATORY EFFICACY ANALYSIS
- 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 (25% vs 18.3%), increased throughout the microtherapy period (week 4: 42.3% vs 29.1%), and persisted in the adjunctive period with concomitant use of TCS (week 6: 81.1% vs 75.1%) (Figure 5).

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

REFERENCES