

# 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

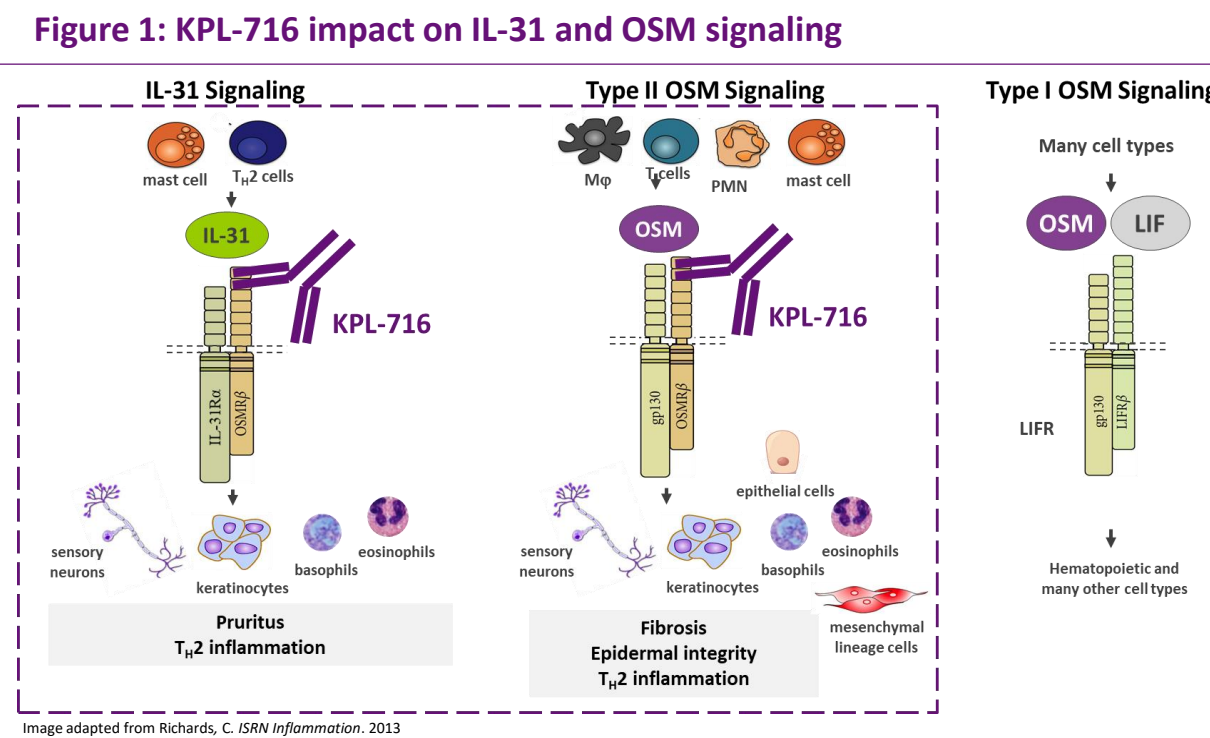
Zamaneh Mikhak<sup>1</sup>, Joel M. Neutel<sup>2</sup>, Robert Bissonnette<sup>3</sup>, Daren Siri<sup>4</sup>, Thomas Wade<sup>5</sup>, Stephen K. Tying<sup>6</sup>, Eben Tessari<sup>1</sup>, Rohan Gandhi<sup>1</sup>, Fang Fang<sup>1</sup>, John F. Paolini<sup>1</sup>

<sup>1</sup>Kiniksa Pharmaceuticals Corp., Lexington, MA; <sup>2</sup>Orange County Research Center, Tustin, CA; <sup>3</sup>Innovaderm Research, Inc., Montreal, Quebec, CAN; <sup>4</sup>Sneeze, Wheeze and Itch Associates, Normal, IL; <sup>5</sup>QPS Miami Research Associates, Miami, FL; <sup>6</sup>Center for Clinical Studies, Department of Dermatology, University of Texas Health Science Center, Houston, TX

## 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)



### 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

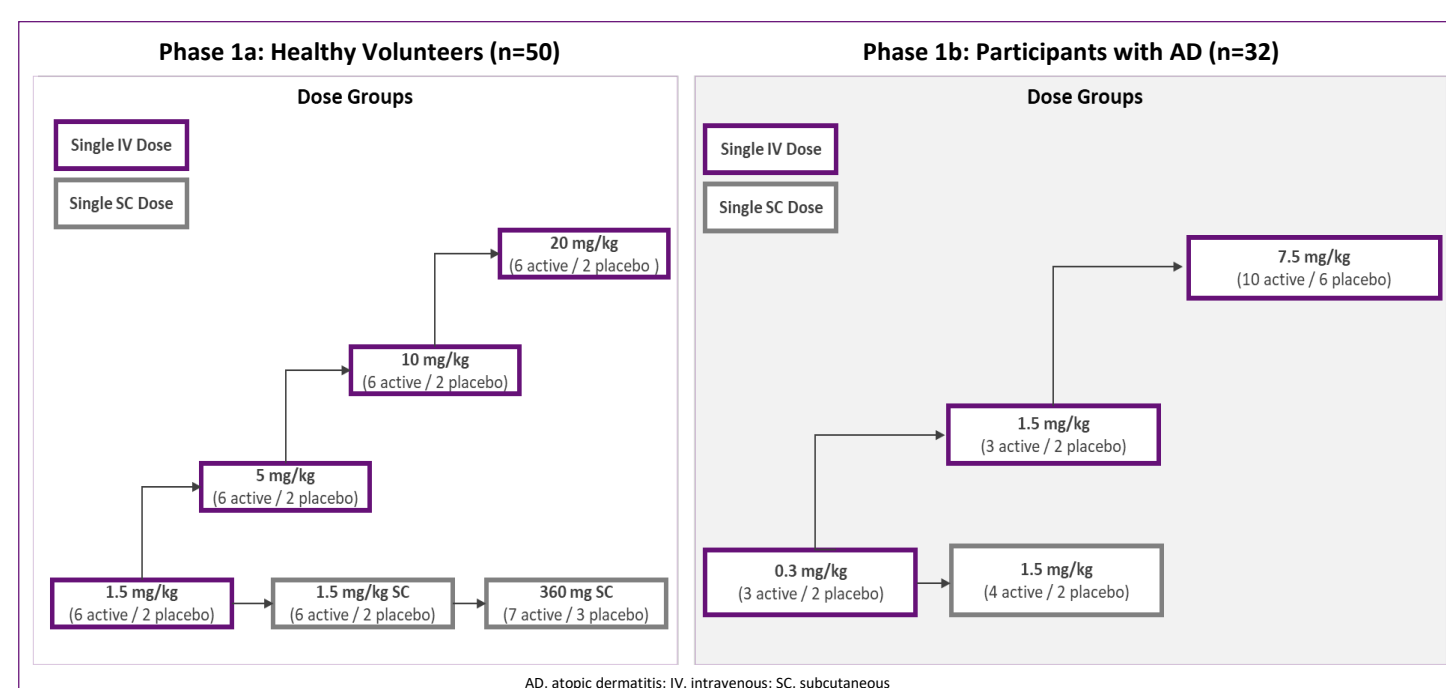
IL-31, an inflammatory cytokine and known pruritogen, has a well-established role in pruritic conditions, including AD	OSM plays an important role in T <sub>H</sub> 2 inflammation, epidermal integrity, and fibrosis
<ul style="list-style-type: none"> <li>IL-31 levels are elevated in AD and correlate with disease severity<sup>1-3</sup></li> <li>Keratinocytes and macrophages express IL-31Rα, and circulating CLA+ T cells express IL-31 in AD<sup>4</sup></li> <li>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<sup>5</sup></li> <li>Anti-IL-31Rα treatment reduces pruritus in AD<sup>6</sup></li> </ul>	<ul style="list-style-type: none"> <li>Increases IL-4Rα and IL-13Rα production<sup>8-13</sup></li> <li>Increases IL-4 production; synergizes with IL-4 and IL-13 to increase eotaxin production in fibroblasts and airway smooth muscle cells<sup>8, 10-14</sup></li> <li>Modulates genes important in keratinocyte activation and differentiation<sup>8, 9</sup></li> <li>Levels are elevated in fibrotic diseases, and OSM over-expression in animal models results in fibrotic changes<sup>11, 15</sup></li> </ul>

## METHODS

### Study Design

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

Figure 2: Phase 1a/1b Study Design



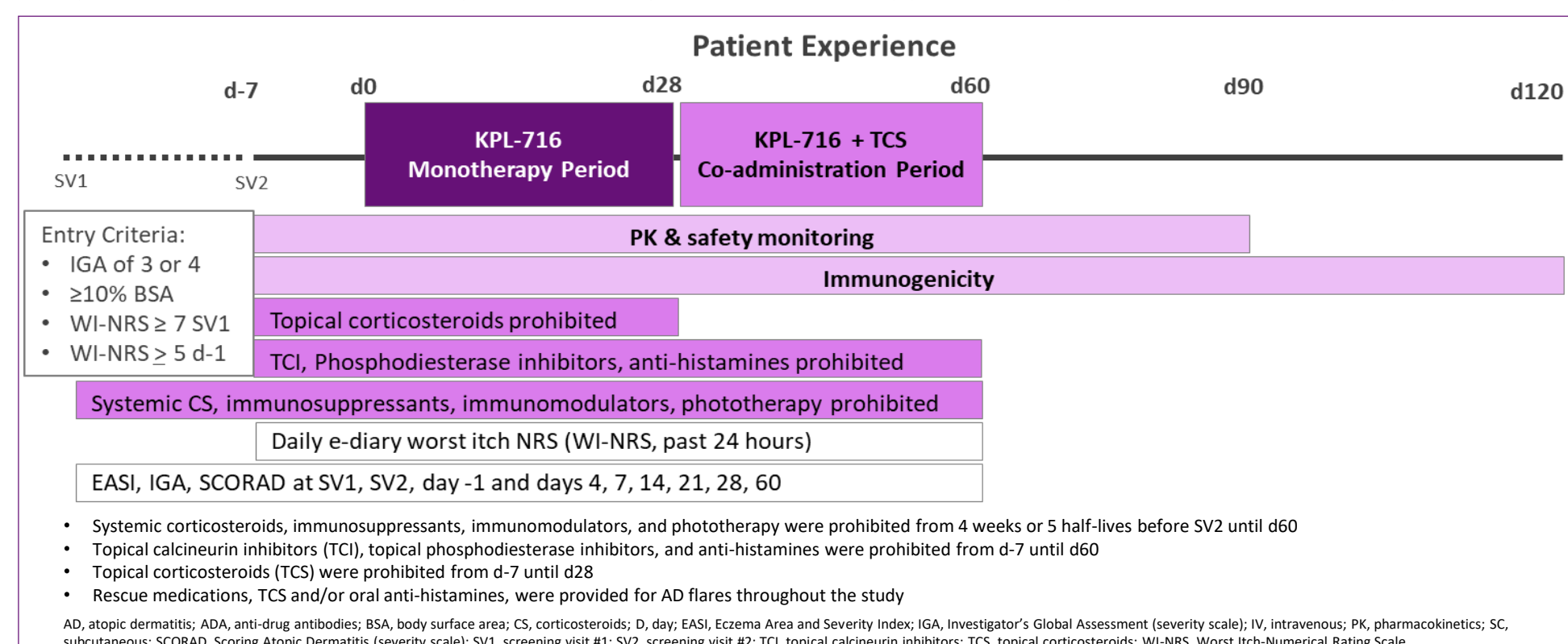
### Objectives

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



## 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)

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)				Placebo (IV)	KPL-716 (SC)		Placebo (SC)
	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 (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

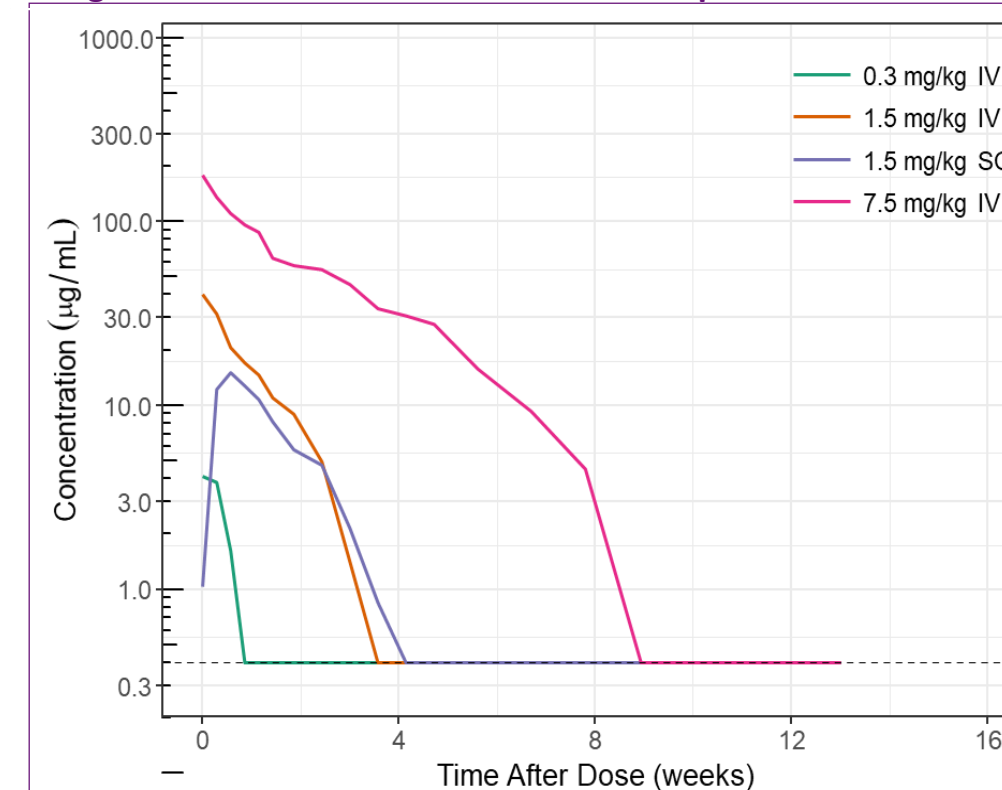
Adverse Event	KPL-716 (IV)			Placebo (SC)	KPL-716 (SC)		Placebo (SC)
	0.3 mg/kg n=3	1.5 mg/kg n=3	7.5 mg/kg n=10	Pooled n=10	1.5 mg/kg n=4	Pooled n=2	Pooled n=5
DR-TEAE	0	Mild headache (1), Decreased appetite (1)	Moderate dizziness (1)	Mild somnolence (1)	Mild dizziness (1)	0	0
AD flare	1	0	2	3	0	0	0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

Figure 4: KPL-716 Demonstrated Dose-Dependent Elimination

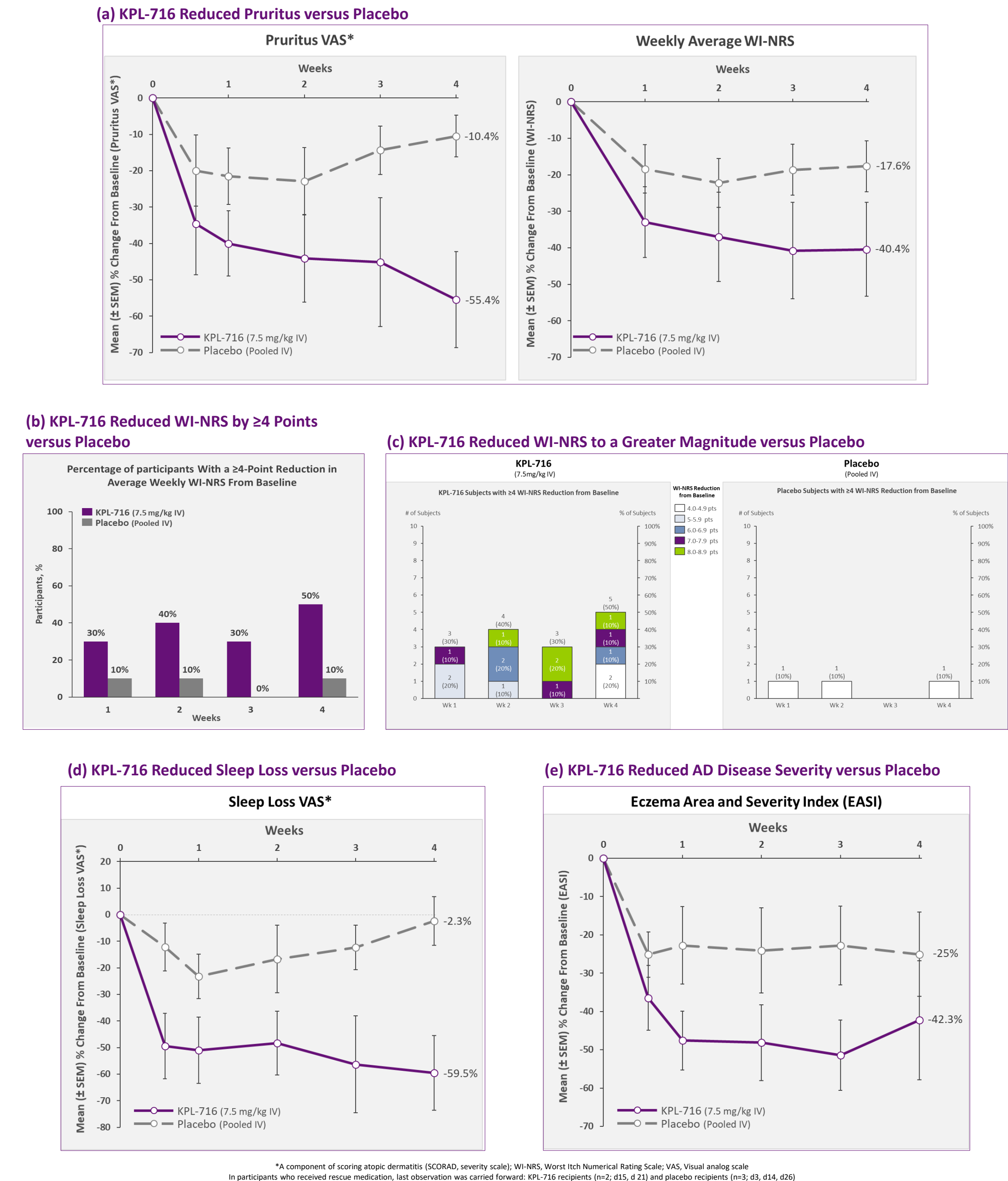


### Phase 1b Exploratory Efficacy

- 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)

## Results (continued)

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



## 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: Study funded by Kiniksa Pharmaceuticals, Ltd. Encore presentation; data originally presented at the 27th European Academy of Dermatology and Venereology (EADV) Congress | 12-16 September 2018 | Paris, FR. Zamaneh Mikhak, Eben Tessari, Rohan Gandhi, Fang Fang, John F. Paolini: Employees at Kiniksa Pharmaceuticals Corp; Joel M. Neutel: Investigator for Kiniksa Pharmaceuticals; Robert Bissonnette: Investigator, Consultant, Advisory Board Member; Speaker for and/or receives honoraria from Aquinos Pharma, Anilobio, Akana, Astellas, Bricebi Biotech, Dermavant, Dermira, Dignity Sciences, Eli Lilly, Galderma, Glenmark, GSK-Steifel, Hoffmann-La Roche Ltd, Leo Pharma, Neokera, Pfizer, Regeneron, Sienna, and Vitae; Shareholder of Innovaderm Research; Investigator for Kiniksa Pharmaceuticals; Daren Siri: Investigator for Regeneron, Pfizer, AnaptysBio, Vanda, Kiniksa Pharmaceuticals, Speaker, Advisory Board, and Steering Committee for Regeneron/Sanofi; Thomas Wade: Investigator for Kiniksa Pharmaceuticals; Stephen K. Tying: Investigator for Abbvie, Aclaris, BMS, BI, Celgene, Dermik, Galderma, GSK, Janssen, Leo, Merck, Novartis, Ortho, Pfizer, Regeneron, Roche, Kiniksa Pharmaceuticals