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

Zamaneh Mikhak[1], Joel M. Neutel[2], Robert Bissonnette[3], Dareen Siri[4], Thomas Wade[5], Stephen K. Tyring[6], Eben Tessari[1], Rohan Gandhi[1], Fang Fang[1], John F. Paolini[1]

[1]Kiniksa Pharmaceuticals Corp., Lexington, Massachusetts, USA; [2]Orange County Research Center, Tustin, California, USA; [3]Innovaderm Research, Inc., Montreal, Quebec, Canada; [4]Sneeze, Wheeze and Itch Associates, Normal, Illinois, USA; [5]QPS Miami Research Associates, Miami, Florida, USA; [6]Houston Skin Associates, Houston, Texas, USA

Presented at: The 27th Congress of the European Academy of Dermatology and Venereology; September 12–16, 2018; Paris, France

Acknowledgements and Disclosures

Acknowledgments:

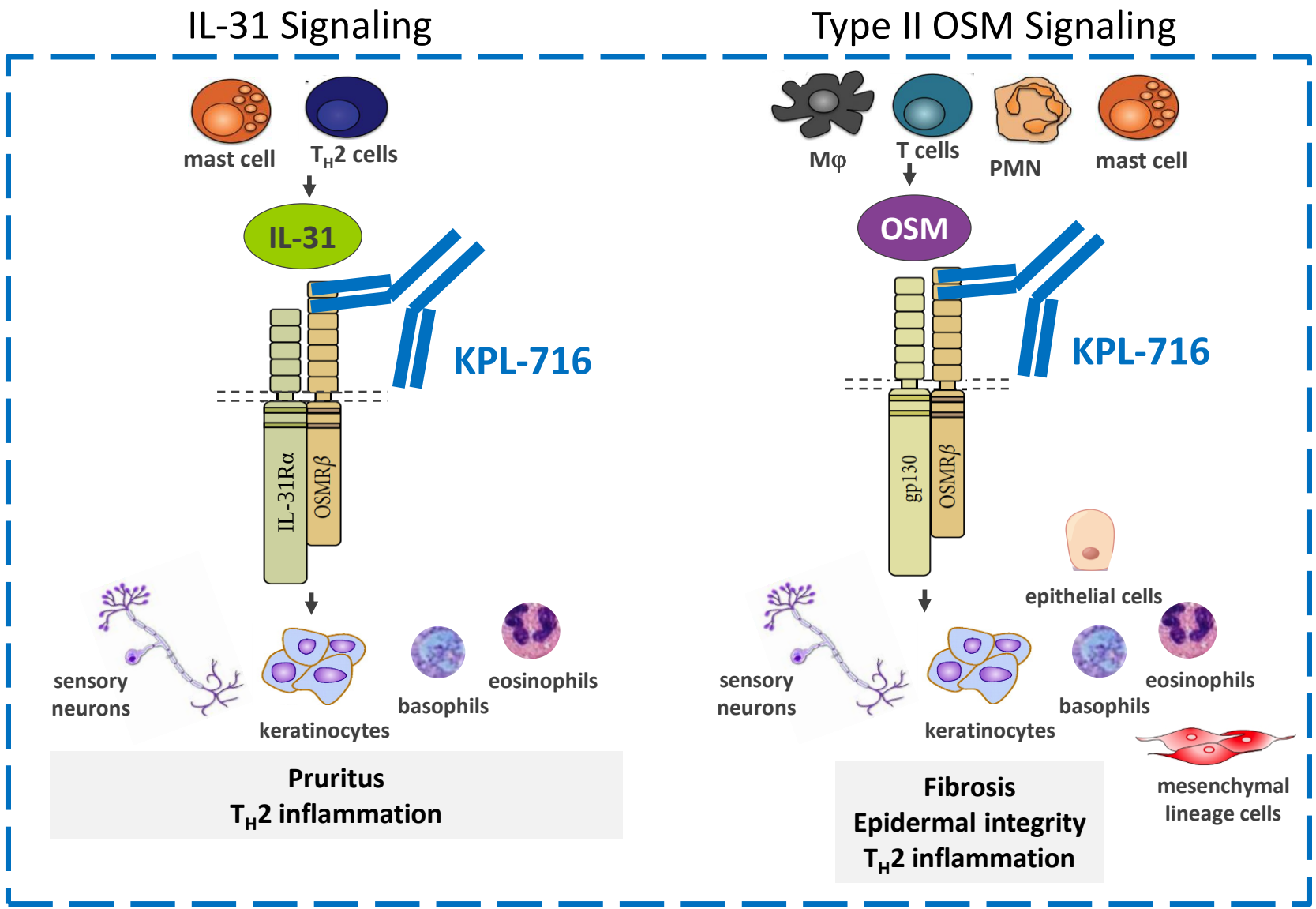
- **Study Sponsor:** Kiniksa Pharmaceuticals, Ltd.

Disclosures:

- **Zamaneh Mikhak, Eben Tessari, Rohan Gandhi, Fang Fang, John F. Paolini:** Employees at Kiniksa Pharmaceuticals Corp.
- **Robert Bissonnette:** Investigator, Consultant, Advisory Board Member, Speaker for and/or receives honoraria from Aquinox Pharma, Antiobix, Asana, Astellas, Brickell Biotech, Dermavant, Dermira, Dignity Sciences, Eli Lilly, Galderma, Glenmark, GSK-Stiefel, Hoffman-LaRoche Ltd, Leo Pharma, Neokera, Pfizer, Regeneron, Sienna, and Vitae; Shareholder of Innovaderm Research; Investigator for Kiniksa Pharmaceuticals, Ltd.
- **Joel M. Neutel:** Investigator for Kiniksa Pharmaceuticals, Ltd.
- **Dareen Siri:** Investigator for Regeneron, Pfizer, AnaptysBio, Vanda, Kiniksa Pharmaceuticals, Ltd., Speaker, Advisory Board, and Steering Committee for Regeneron /Sanofi.
- **Stephen K. Tyring:** Investigator for Abbvie, Aclaris, BMS, BI, Celgene, Dermik, Galderma, GSK, Janssen, Leo, Merck, Novartis, Ortho, Pfizer, Regeneron, Roche, Kiniksa Pharmaceuticals, Ltd.
- **Thomas Wade:** Investigator for Kiniksa Pharmaceuticals, Ltd.

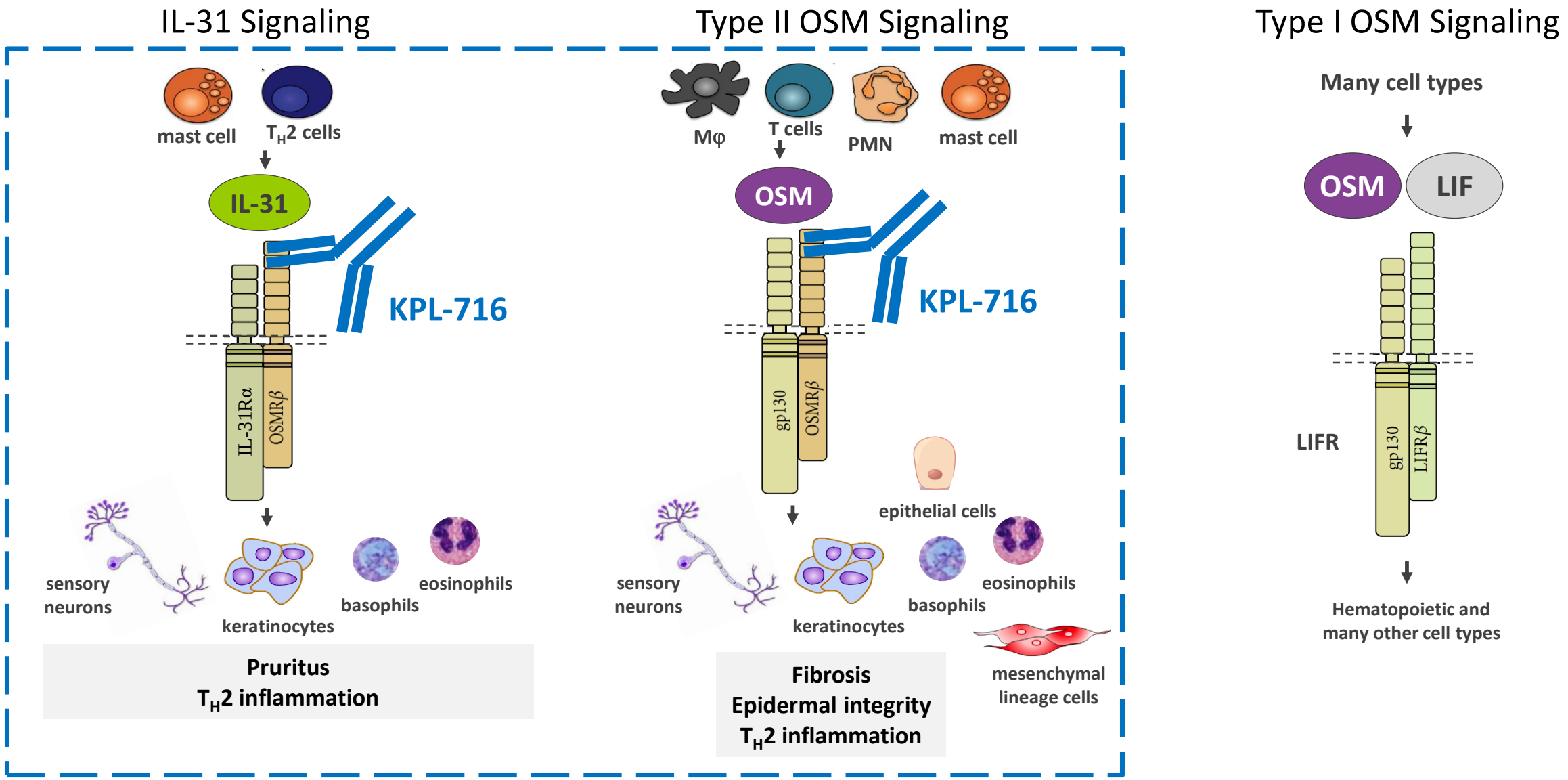
2

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



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-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 reduced pruritus in AD[6]

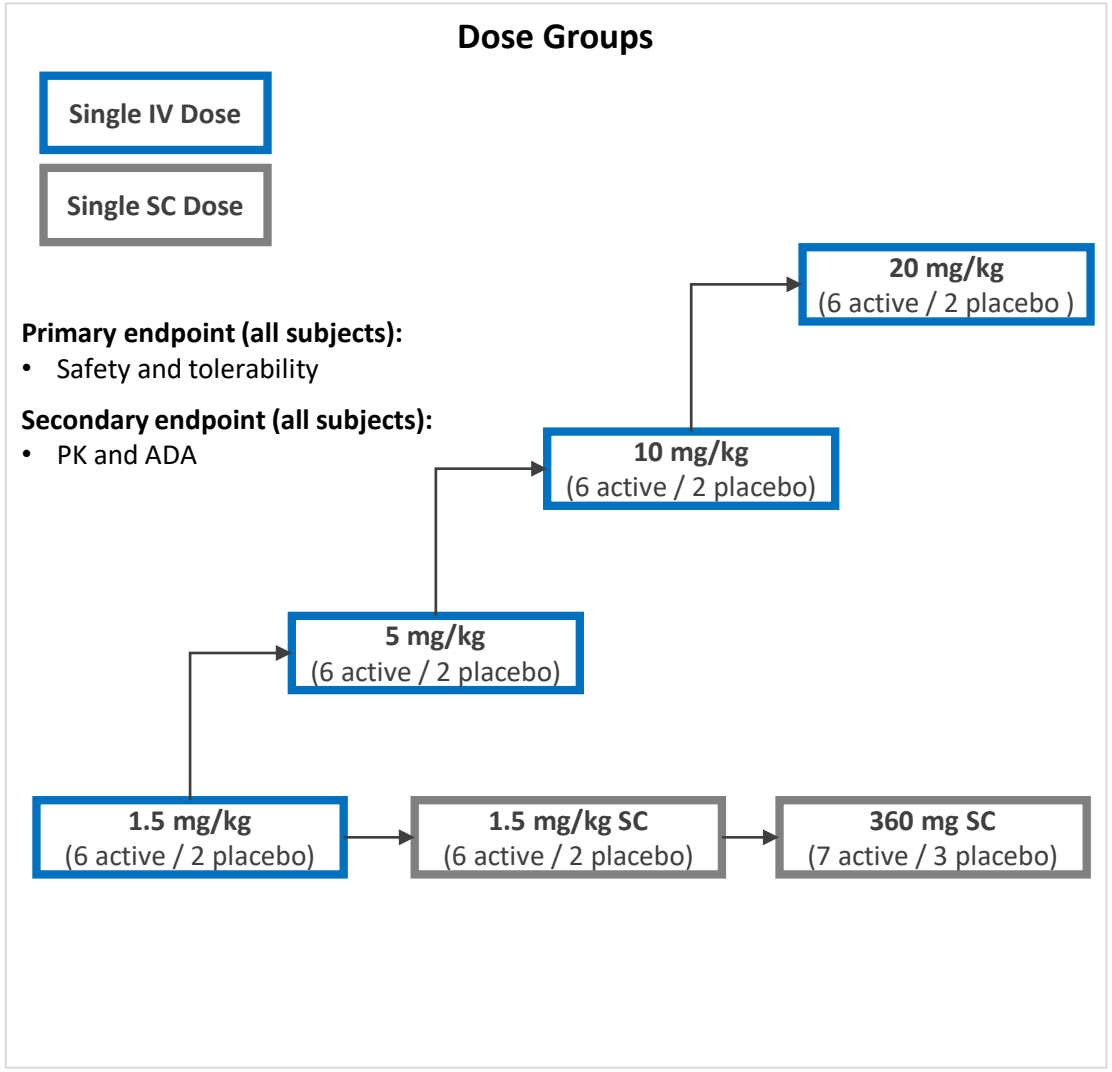
OSM plays an important role in T_H2 inflammation, epidermal integrity, and fibrosis

- 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]

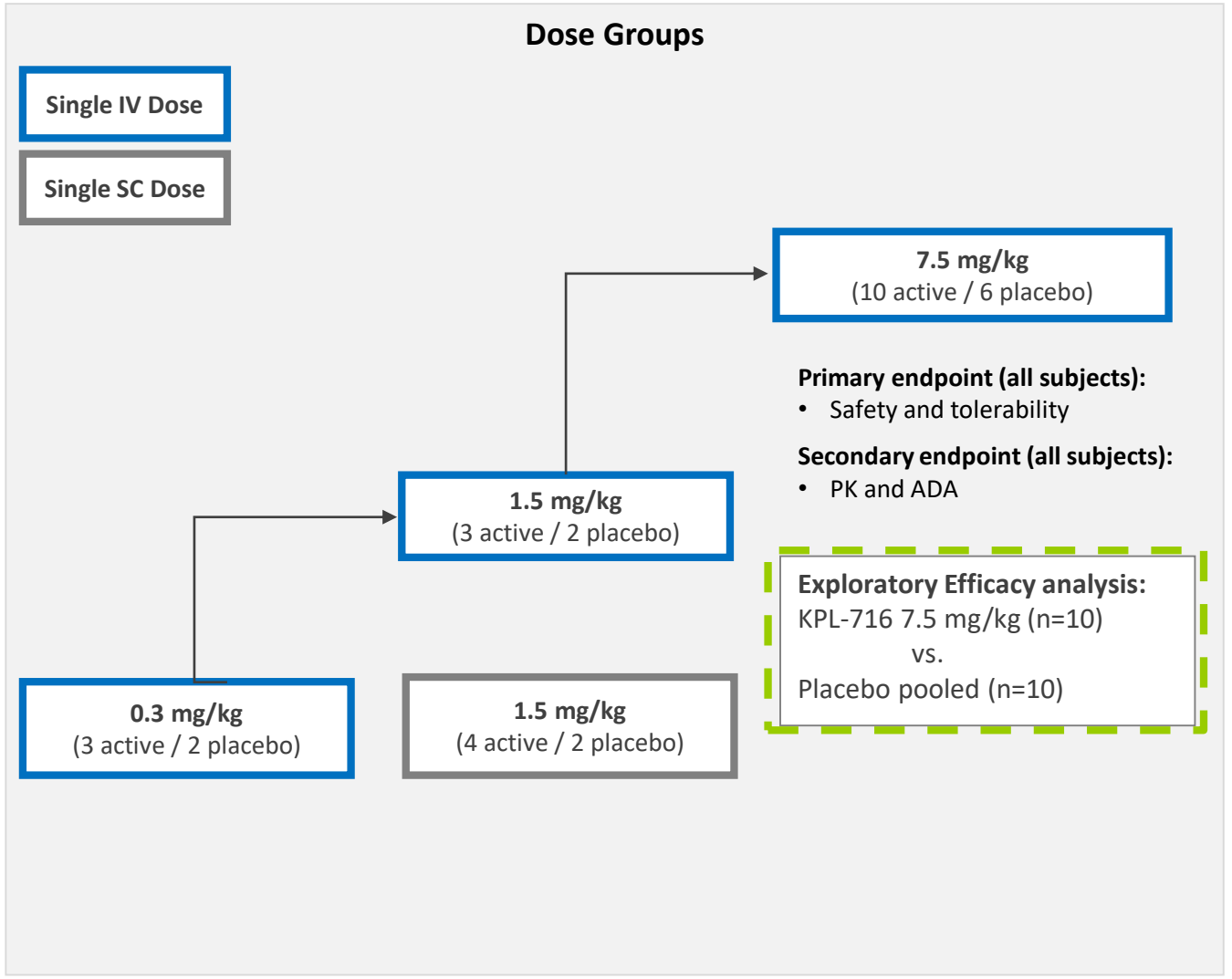
1) Raap et al. JACI, 2008; 2) Kim et al. Ann Derm, 2011; 3) Nobbe et al. Acta Derm Venerol, 2012; 4) Bilsborough et al. JACI, 2006; 5) Raap et al. Clin Exp Allergy, 2017; 6) Nemoto et al. BJD, 2016; 7) Ruzicka et al. JEM, 2017; 8) Gazel et al. JID, 2006; 9) Boniface et al. JI, 2007; 10) Fritz et al. JI, 2011; 11) Mozaffarian et al. JI, 2008; 12) Fritz et al. Exp Cell Rsch, 2009; 13) Kwofie et al. Resp Rsch, 2015. 14) Botelho et al. JI, 2013; 15) Wong et al. Lab Investigation; 2014.

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

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



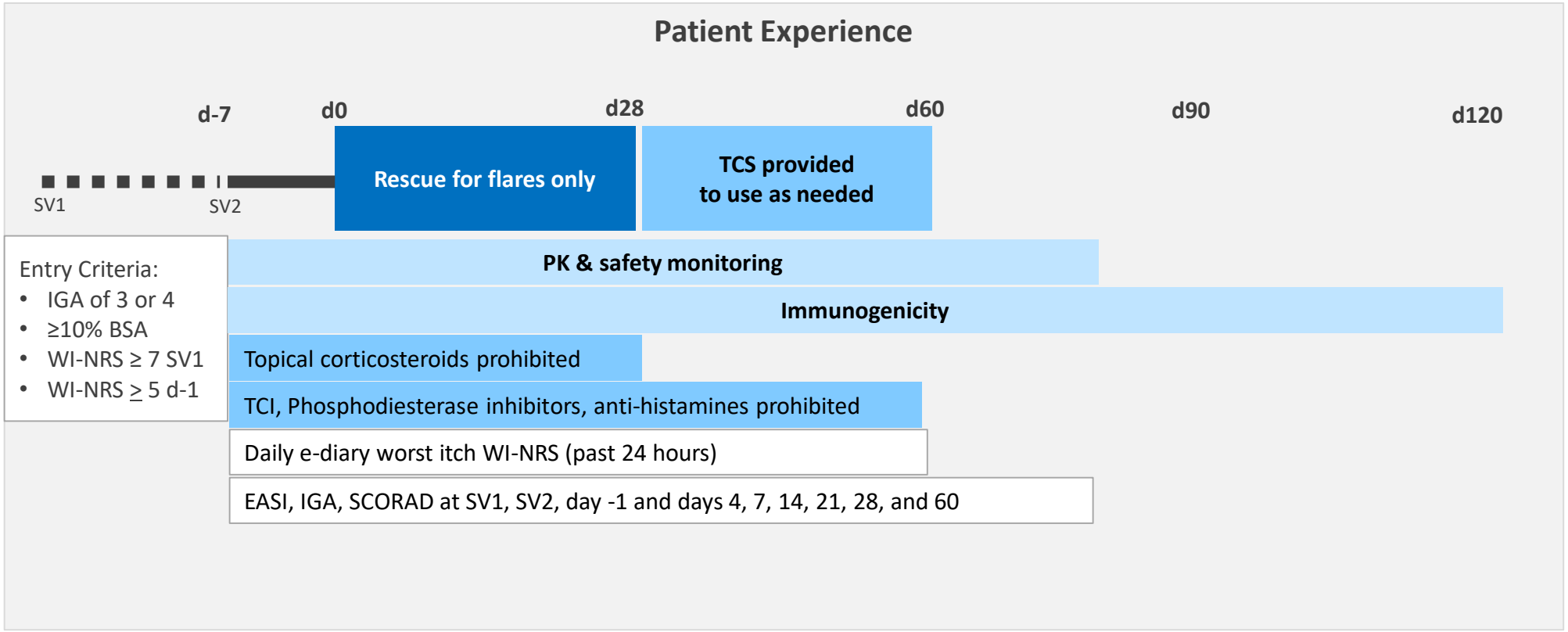
Phase 1b: Subjects with AD (n=32)



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)



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

Baseline demographics/disease characteristics: AD	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)	60.7 (13.7)
IGA=3, %	80	80
IGA=4, %	20	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)

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

Healthy volunteers

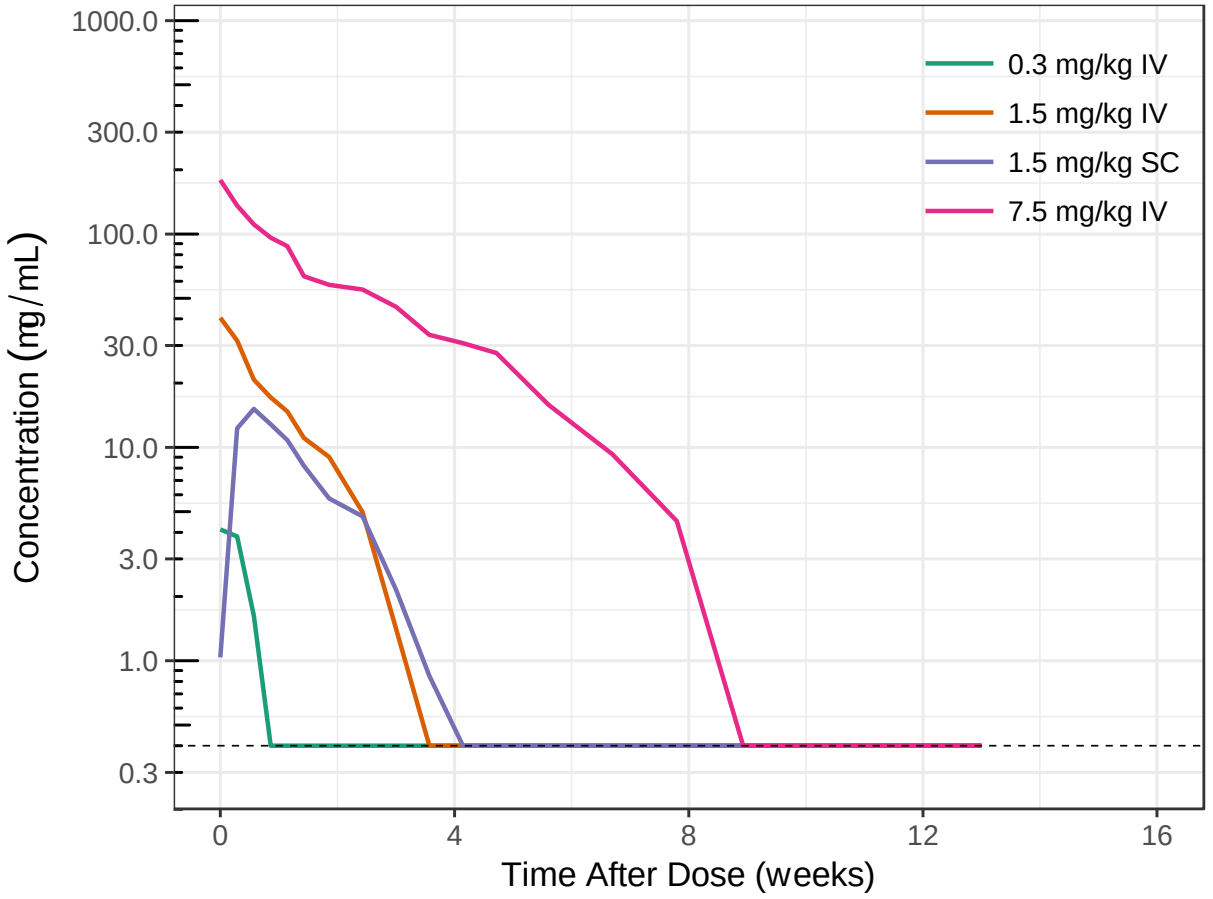
AE	KPL-716 (IV)				Placebo (IV)	KPL-716 (SC)		Placebo (SC)
	1.5 mg/kg n=6	5 mg/kg n=6	10 mg/kg n=6	20 mg/kg n=6	Pooled n=8	1.5 mg/kg n=6	360 mg n=7	Pooled n=5
DR-TEAE	0	Mild headache (1)	0	0	0	Mild flushing (1)	Mild anemia (1)	0

Subjects with atopic dermatitis

AE	KPL-716 (IV)			Placebo (IV)	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
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

†The only moderate DR-TEAE occurred after a protocol violation.

KPL-716 demonstrated dose-dependent elimination (TMDD)



TMDD: Target-Mediated Drug Disposition

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

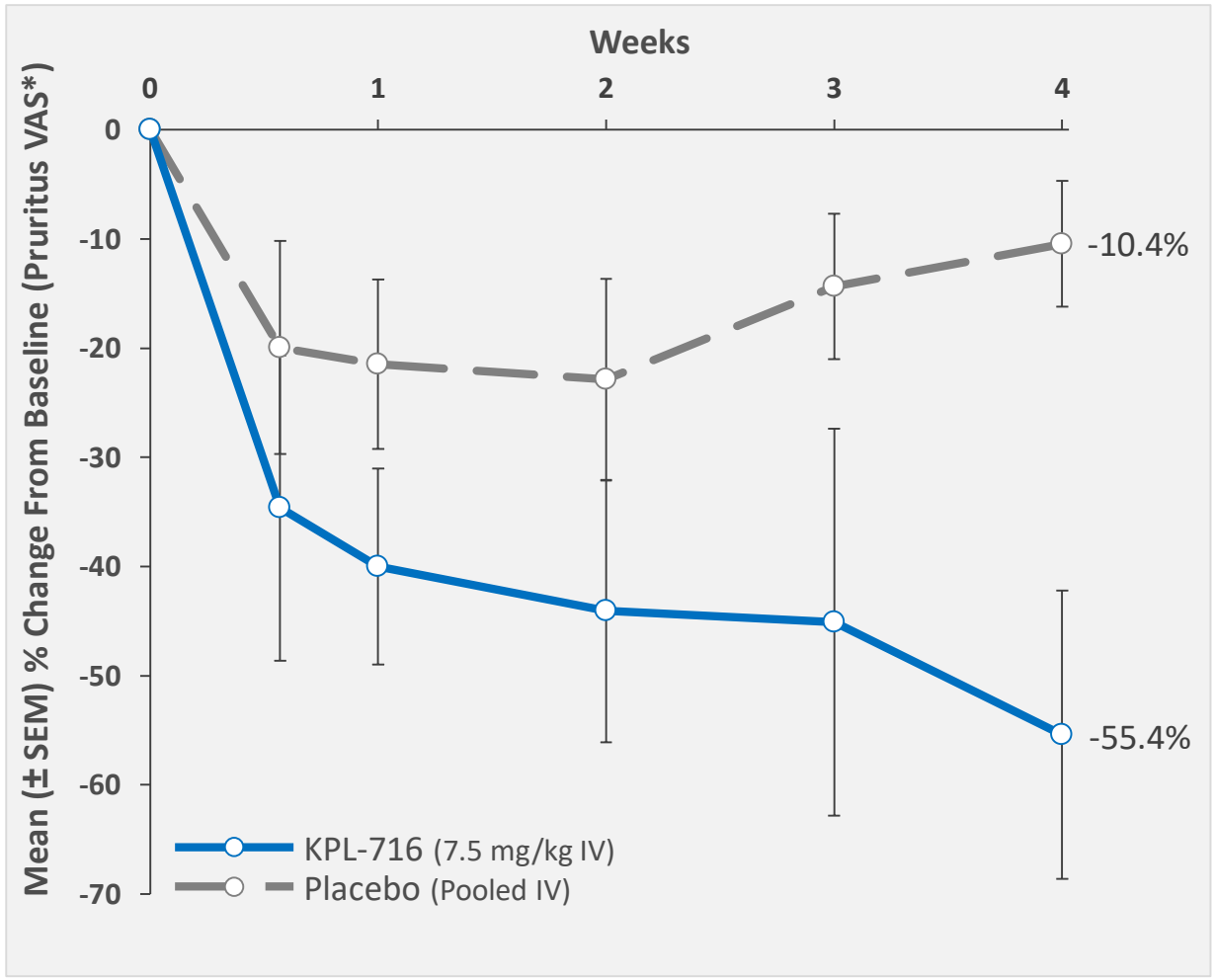
Efficacy Endpoints:

- 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)

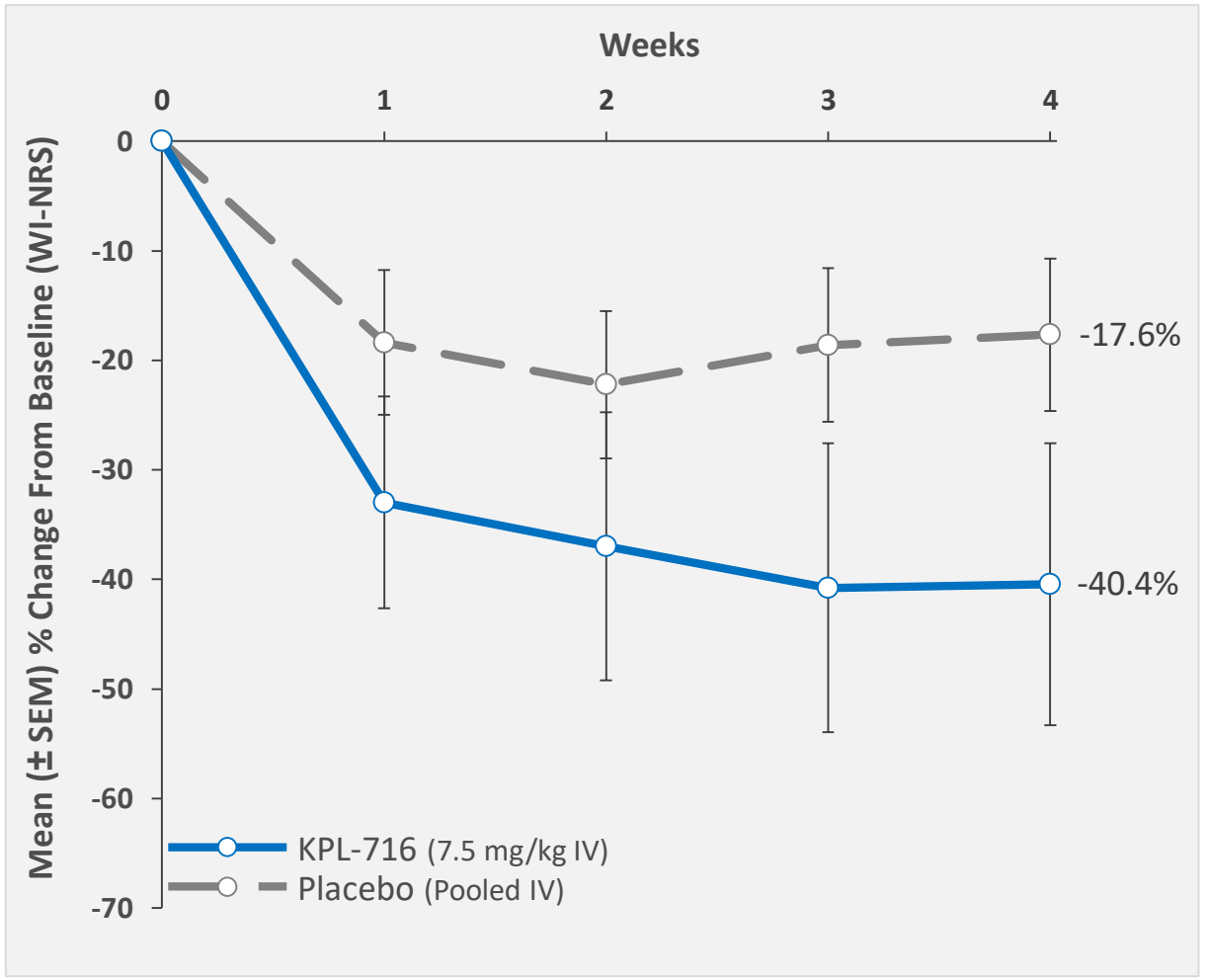
AD = atopic dermatitis, IV = intravenous, WI-NRS = Worst Itch Numerical Rating Scale,
EASI = Eczema Area and Severity Index, SCORAD = Scoring atopic dermatitis (severity scale)

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)

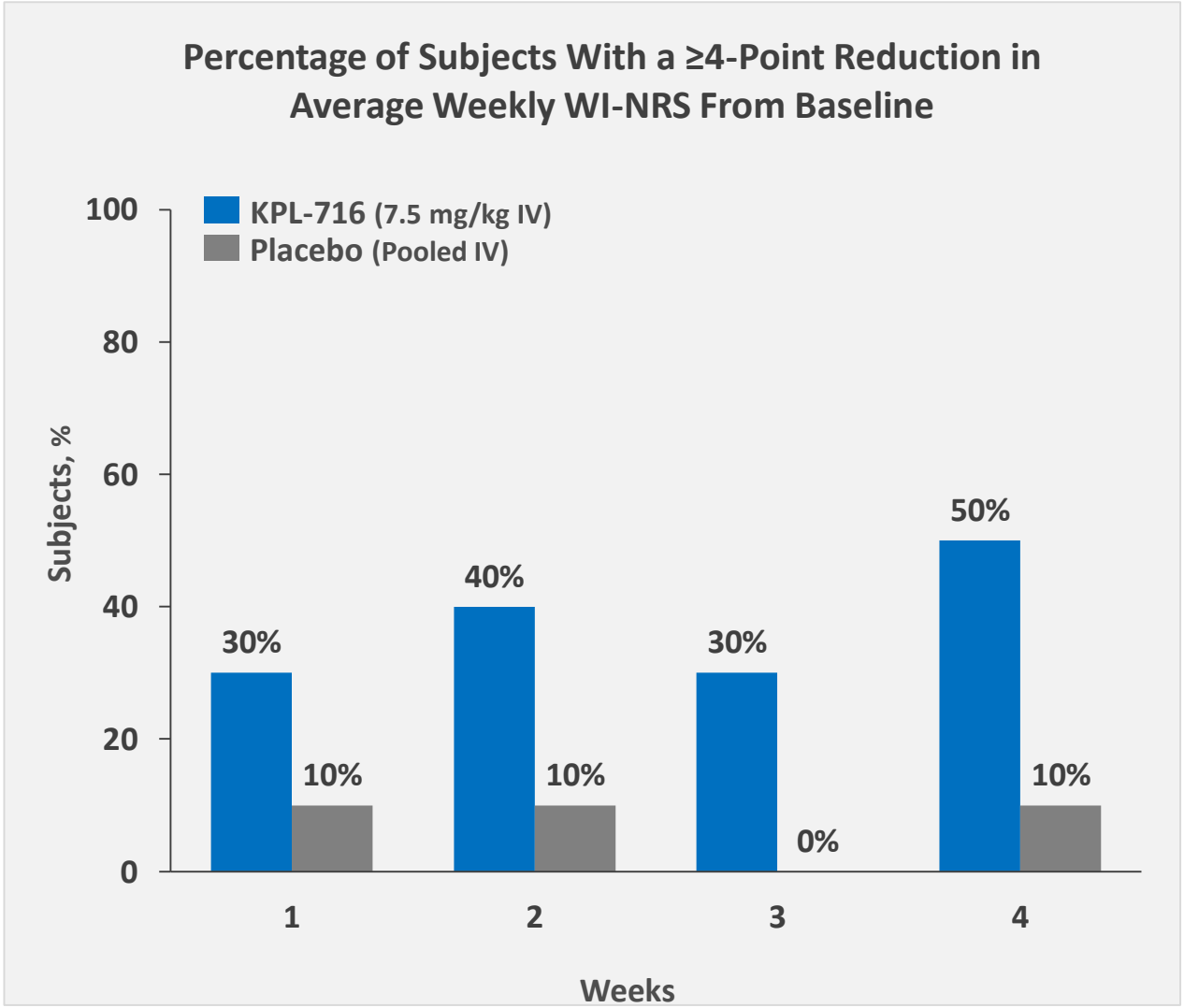


*A component of SCORAD.

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).

SCORAD = Scoring atopic dermatitis (severity scale)

KPL-716 (single dose) reduced WI-NRS by ≥4 Points versus Placebo
(28 day monotherapy period)



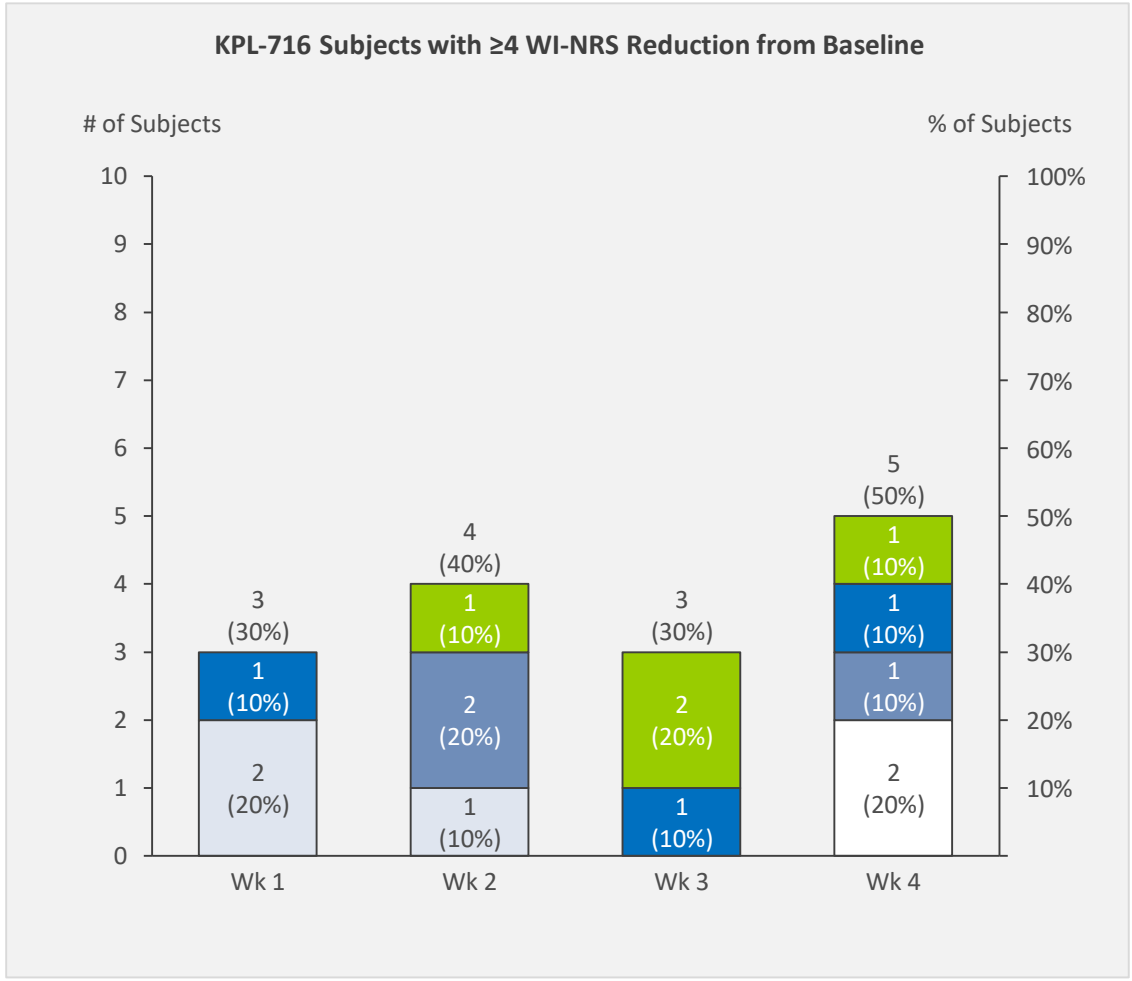
Subject was considered non-responder after rescue. Two KPL-716 recipients (d15, d 21) and three placebo recipients (d3, d14, d26).

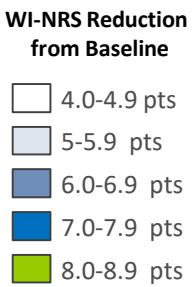
WI-NRS = Worst Itch Numerical Rating Scale

KPL-716 (single dose) reduced WI-NRS to a greater magnitude versus Placebo

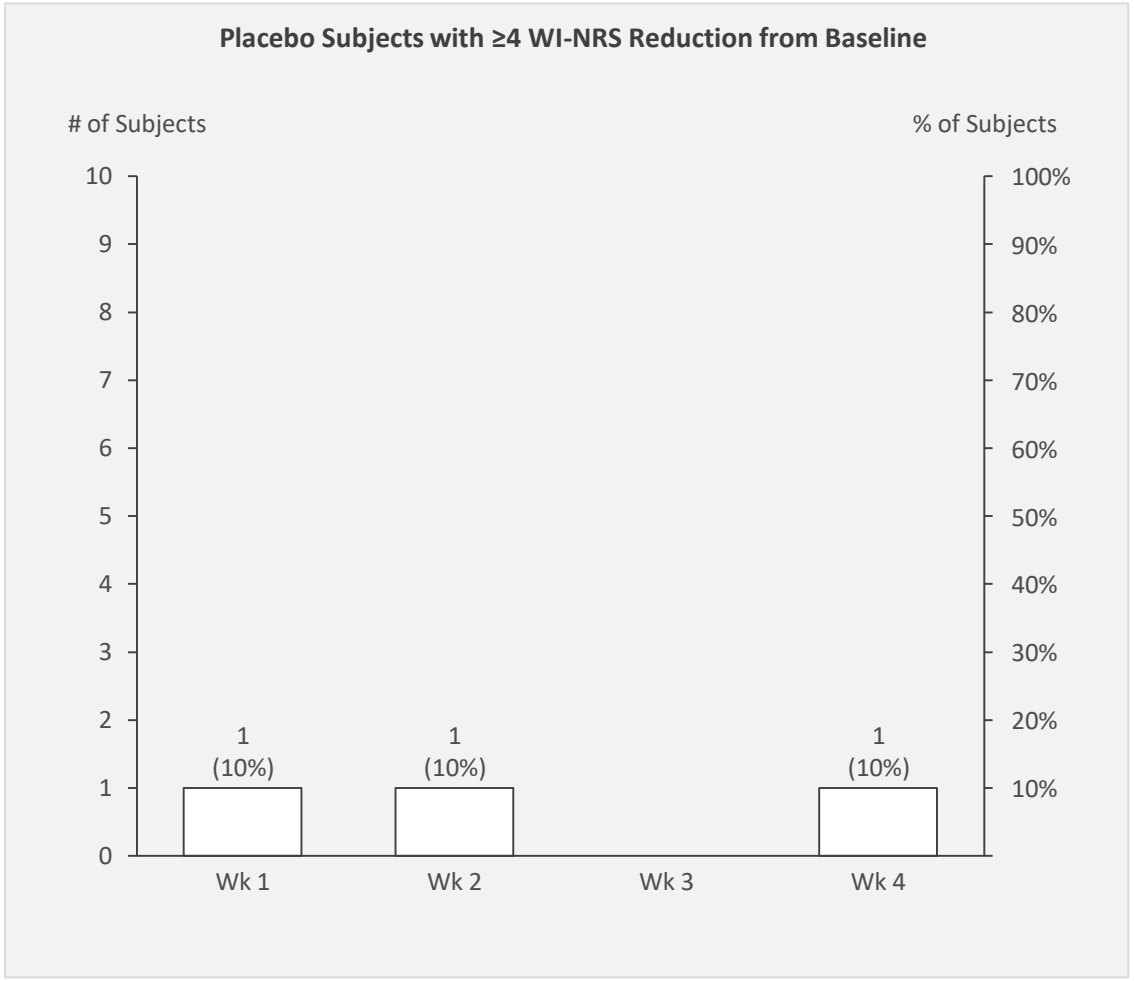
(28 day monotherapy period)

KPL-716
(7.5mg/kg IV)





Placebo
(Pooled IV)



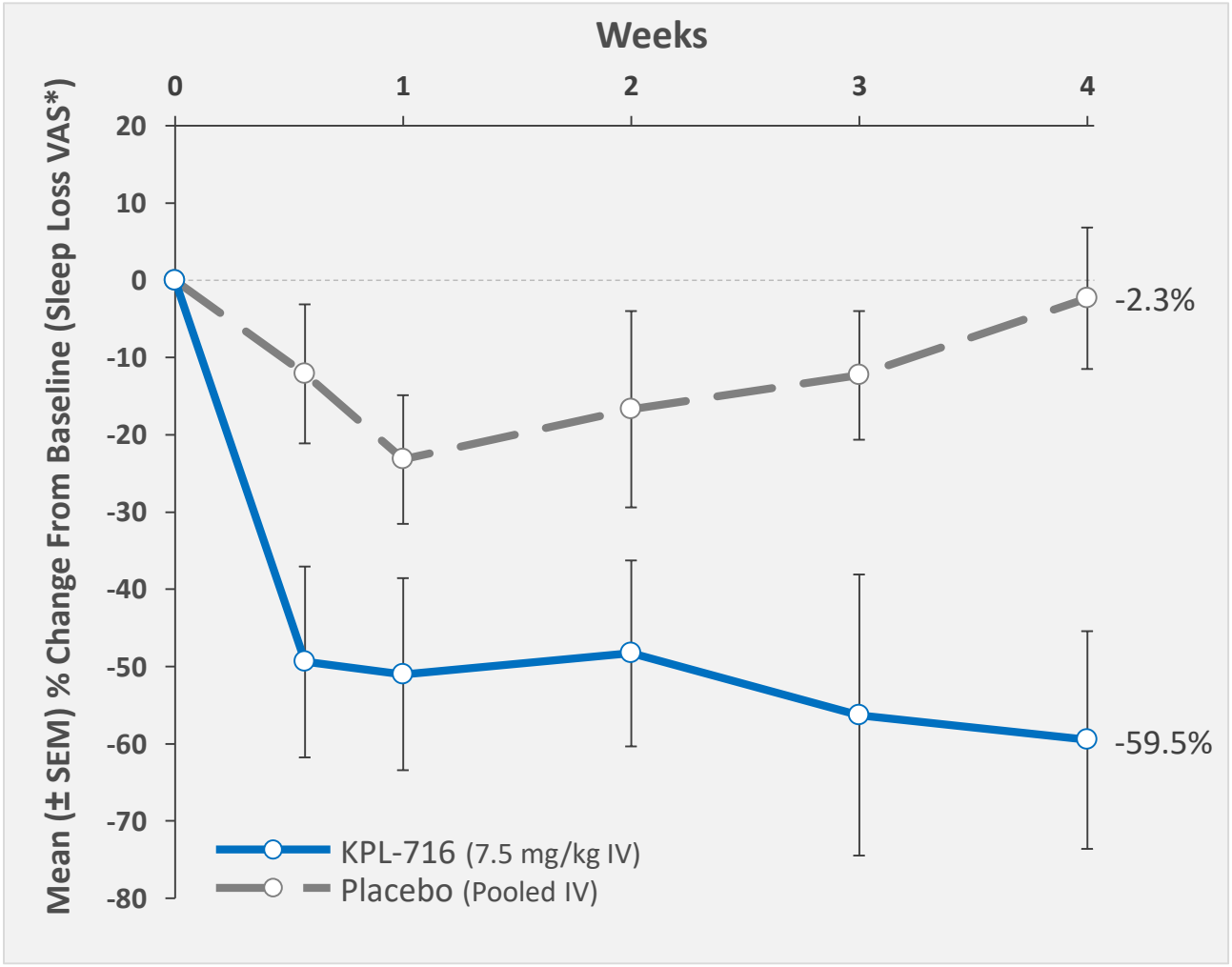
Subject was considered non-responder after rescue. Two KPL-716 recipients (d15, d 21) and three placebo recipients (d3, d14, d26).

WI-NRS = Worst Itch Numerical Rating Scale

KPL-716 (single dose) reduced Sleep Loss, an important QoL parameter, versus Placebo

(28 day monotherapy period)

Sleep Loss VAS*



*A component of SCORAD.

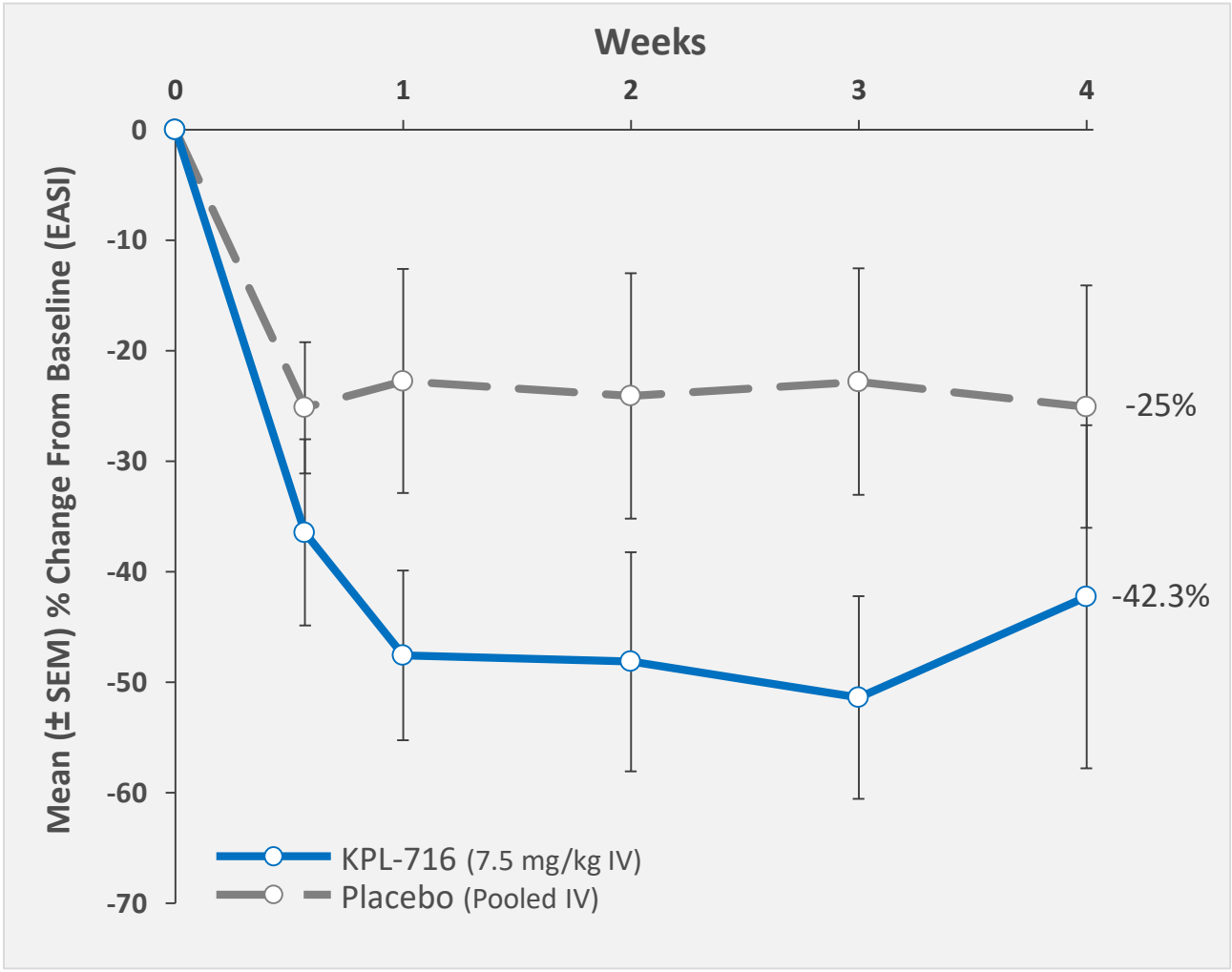
In subjects who received rescue medication, last observation was carried forward. Two KPL-716 recipients (d15, d 21) and three placebo recipients (d3, d14, d26).

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, d 21) 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

Thank You to the Patients, Investigators and Study Staff

Joel M. Neutel, MD
Orange Country Research Center
Tustin, California, USA

Thomas Wade, MD
QPS-MRA, LLC
Miami, Florida, USA

Douglas Denham, DO, CPI
Clinical Trials of Texas, Inc.
San Antonio, Texas, USA

Robert Bissonnette, MD
Innovaderm
Montreal, Quebec, Canada

Dareen Siri, MD
Sneeze, Wheeze and Itch Associates
Normal, Illinois, USA

Jamshid Lofti, MD
Clinical Trial Network
Houston, Texas, USA

Stephen K. Tyring, MD
Houston Skin Associates
Houston, Texas, USA

Iftikhar Hussain, MD
Vital Prospects
Tulsa, Oklahoma, USA

Jonathan S. Dosik, MD
TKL Research
Fair Lawn, New Jersey, USA