1002

KPL-716, an Anti–oncostatin M Receptor Beta (OSMRβ) Monoclonal Antibody, Reduces IL-31–Induced Scratching Behavior in Cynomolgus Monkeys: Establishment and Optimization of a Pharmacokinetic/Pharmacodynamic Model

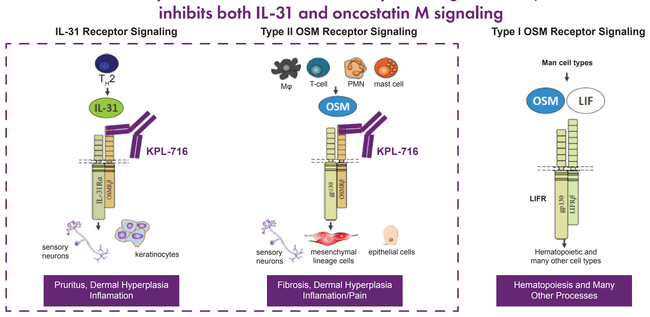
Rohan Gandhi,[1] Karalyne Crowder,[2] Kory Barrow,[2] Moses Njenga,[1] Thomas Prod'homme,[1] John F. Paolini[1]

[1]Kiniksa Pharmaceuticals Corp., Lexington, MA, USA; [2]Altasciences Preclinical Seattle LLC, Everett, WA, USA

BACKGROUND

- Interleukin 31 (IL-31) signals through the heterodimer complex consisting of IL-31 receptor alpha (IL-31Rα) and oncostatin M receptor beta (OSMRβ)[1,2] (**Figure 1**)
- IL-31 is produced by activated CD4+ T cells, primarily T_H2 helper cells, macrophages, and dendritic cells[3,4]
- IL-31 and its receptor complex induce pruritic skin disease, including atopic dermatitis and chronic urticaria[3,5,6]
- KPL-716 is a fully human monoclonal antibody that targets OSMRβ and simultaneously inhibits both IL-31 and oncostatin M signaling (**Figure 1**)[7]
- Animal models have been developed that demonstrate the pruritogenic effects of IL-31 and are useful to demonstrate biologic activity of potential therapeutic agents[1,8,9]

Figure 1. KPL-716 is a fully human monoclonal antibody that targets OSMRβ and simultaneously inhibits both IL-31 and oncostatin M signaling



OSMRβ, oncostatin M receptor beta; PMN, polymorphonuclear cell; T_H2, T helper type 2.
Image adapted from Richards C. *ISRN Inflammation*. 2013;2013:1-23.[2]

OBJECTIVES

- To determine the optimal intradermal (ID) dose of recombinant human IL-31 demonstrating a consistent and robust scratching response in cynomolgus monkeys
- To establish in vivo proof of on-target efficacy of KPL-716 and the correlation between pharmacokinetics (PK) and pharmacodynamics (PD) to determine an efficacious concentration range for KPL-716 in this animal model
  - Following a single intravenous (IV) dose
  - In a repeated challenge model
- To compare the efficacy of KPL-716 by subcutaneous (SC) and IV administration
  - To determine the repeated-dose KPL-716 SC dose/interval that inhibits IL-31–induced pruritus

METHODS

Optimization of the model

- 16 animals were randomized to 4 IL-31 dose groups: 3, 6, 12, and 24 µg/kg in a weight-stratified manner
- IL-31 (derived from *Escherichia coli*; R&D Systems, Minneapolis, MN) was administered ID on day 1

Single-dose PK/PD

- 24 animals were assigned to 4 groups of 6 animals each (**Table 1**)
- KPL-716 (1, 3, and 10 mg/kg) or control was administered by IV injection on day 1
- IL-31 was administered ID once during acclimation and on days 2 (24 hours after KPL-716), 8, 15, 22, and 29

Table 1. Dose groups for single-dose PK/PD study

KPL-716 (mg/kg) IV Day 1	IL-31 (µg/kg) ID Days 2, 8, 15, 22, 29	Male Cynomolgus Monkeys (n)[a]
0	3	6
1	3	6
3	3	6
10	3	6

[a]The 16 monkeys used for optimization were assigned a different IL-31 challenge dose for the PK/PD study, and the remaining 8 animals were randomized into groups stratified by body weight. ID, intradermal; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics.

IV to SC bridge mini-PK

- 18 animals were assigned to 6 groups of 3 animals each
- KPL-716 (1, 3, and 8 mg/kg) was administered by IV and SC route

Repeat-dosing PK/PD

- 36 animals were assigned to 6 groups of 6 animals each
- KPL-716 (1, 2, 3, and 8 mg/kg) or control was administered by either SC or IV route (**Table 2**)
- IL-31 was administered ID at various time points as shown in **Table 2**

Assessments

- On each day of IL-31 ID administration, observations of pruritic response, including scratching and grooming behaviors, were documented using the Noldus MediaRecorder (Leesburg, VA) for ≥1 hour prior to IL-31 dosing and ≥1 hour after dosing, beginning 30 minutes postdose
- Blood samples were collected 2.5 hours post–IL-31 injection on days −1, 2, 8, 15, 22, and 29
- Body weight was routinely monitored

Data analysis

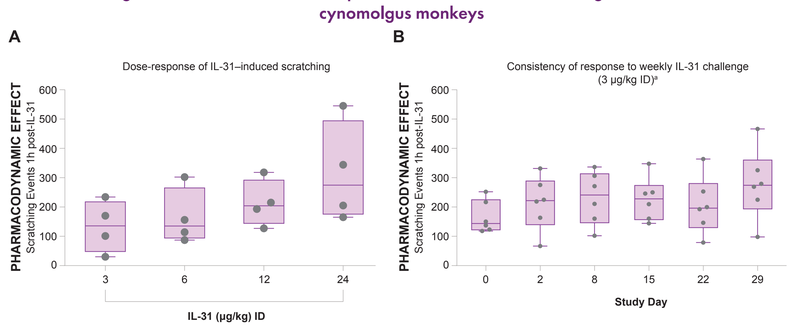
- Scratching events were reported as the number of events post–IL-31 challenge minus pre–IL-31 challenge

RESULTS

Optimization of the model (Figure 2)

- IL-31 invoked a scratching response in all animals; magnitude of response and variability tended to increase with increasing IL-31 dose
- Weekly responses to serial IL-31 challenge remained constant over time
- The 24-µg/kg IL-31 dose was most variable; 3 µg/kg was chosen for subsequent experiments

Figure 2. IL-31 induces dose-dependent and consistent scratching behavior in cynomolgus monkeys

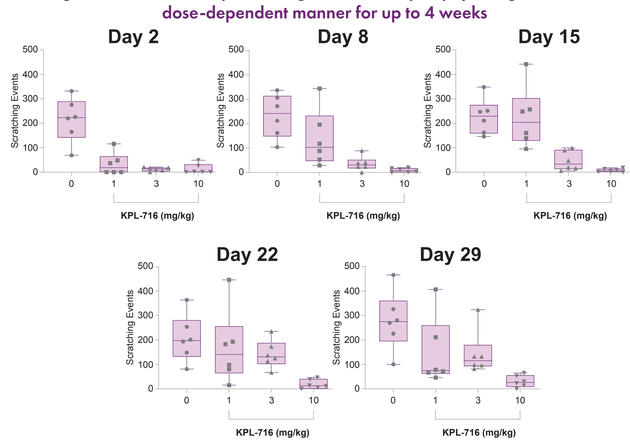


Events are calculated as post–IL-31 challenge minus pre–IL-31 challenge events. Boxes and whisker plots indicate data points for each animal in each dose group; the median is represented by a horizontal line within the box, and the box itself represents the interquartile range. ID, intradermal.
[a]Scratching events recorded in animals receiving control (ie, KPL-716 0 mg/kg).

Single IV dose (Figure 3)

- Single-dose KPL-716 IV attenuated IL-31–induced scratching in a dose- and time-dependent manner
- At day 2, all doses of KPL-716 reduced scratching compared to acclimation and control
- KPL-716 1 mg/kg IV was effective 24 hours post administration, and its effect waned by day 8
- KPL-716 3 mg/kg IV maintained an antipruritic effect through day 15
- KPL-716 10 mg/kg IV maintained an antipruritic effect through day 29

Figure 3. Single-dose IV KPL-716 protects against serial supra-physiologic IL-31 challenge in a dose-dependent manner for up to 4 weeks

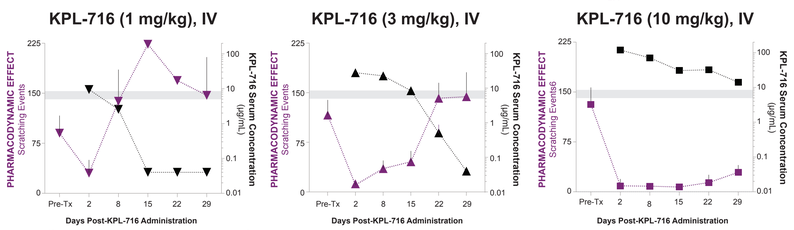


KPL-716 was administered intravenously (IV) on day 1.
Scratching events are calculated as post–IL-31 challenge minus pre–IL-31 challenge events. Boxes and whisker plots indicate data points for each animal in each dose group; the median is represented by a horizontal line within the box, and the box itself represents the interquartile range.

PK/PD correlation (Figure 4)

- KPL-716 plasma concentrations correlated with a reduction in scratching events
- The efficacious concentration of KPL-716 in this model was 5 to 8.5 µg/mL
  - TMDD threshold was established at ≥10 µg/mL
- KPL-716 exposure increased with increasing dose

Figure 4. Correlation between pharmacokinetics and pharmacodynamics following a single IV dose of KPL-716: determination of efficacious concentration (C_{EFF})



Efficacious concentration defined via PK/PD correlation = 5 to 8.5 µg/mL.
KPL-716 was administered intravenously (IV) on day 1; 6 animals were treated per dose group. Scratching events are calculated as post–IL-31 challenge minus pre–IL-31 challenge events. Lower limit of quantification = 0.04 µg/mL.

Table 2. Study design for repeated-dose (IV and SC) PK/PD study

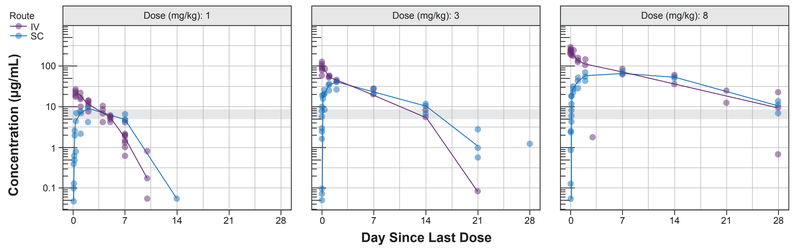
Days	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
G1 (0 mg/kg SC)	B	D	CB						DB		C					DB			C				DB				C			DB						C		D								
G2 (1 mg/kg SC)	B	D	CB						DB		C				C	DB			C				DB				C			DB						C		D								
G3 (2 mg/kg SC)	B	D	CB						B						C	DB							B							DB	C														C
G4 (3 mg/kg IV)	B	D	CB						B						C	B							DB							B							C								C
G5 (3 mg/kg SC)	B	D	CB						B							DB							B				C			DB															C
G6 (8 mg/kg SC)	B	D	CB						B							B							B				C			DB		C													C

D = KPL-716 dosing
C = IL-31 challenge dose (3 µg/kg) and observation for scratching/grooming events (pruritus; pharmacodynamic [PD] effect)
B = blood collection for pharmacokinetic (PK) analysis
IV, intravenous; IL-31, recombinant human interleukin 31; SC, subcutaneous.

IV to SC bridge (Figure 5)

- High bioavailability was observed at SC doses ≥3 mg/kg

Figure 5. IV to SC conversion predictions: KPL-716 3 mg/kg SC every 2 weeks or 8 mg/kg SC every 4 weeks should provide protection from IL-31–induced pruritus



Efficacious concentration defined via PK/PD correlation = 5 to 8.5 µg/mL. IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous.

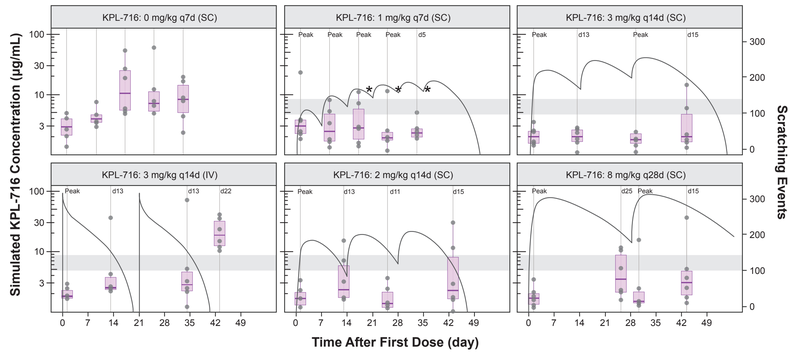
Dose (mg/kg)	Route	C_{max} (CV%) (µg/mL)	T_{max} [c] (hours)	AUC_{last} (CV%) µg•h/mL	AUC_{inf} (CV%) µg•h/mL	F
1	IV	19.73 (5.6)	8.01 (7.93-8.03)[b]	1569.63 (15.4)	1570.81 (15.4)	-
1	SC	6.77 (38.3)	72 (72-96)	1041.79 (33.5)	1044.01 (33.3)	0.66
3	IV	68.77 (1.9)	0.08 (0.08)	9353.62 (4.4)	9354.92 (4.4)	-
3	SC	39.08 (15.5)	72 (72-144)	10,585.36 (12.2)	10,586.92 (12.2)	1.13
8	IV	180.80 (3.3)	0.08 (0.08)	34,139.57 (9.9)	34,140.85 (9.9)	-
8	SC	79.06 (6.9)	120 (120-144)	30,235.42 (1.6)	30,236.86 (1.6)	0.89

KPL-716 was administered on day 0; 3 animals were treated per treatment group; lower limit of quantification = 0.04 µg/mL.
AUC_{inf}, area under the curve from time 0 to infinity; AUC_{last}, area under the curve from time 0 to last measurable concentration; C_{max}, maximum concentration; F, bioavailability; IV, intravenous; SC, subcutaneous; T_{max}, time to achieve C_{max}.
[c]Median and range shown for T_{max}; mean values are shown for C_{max}, AUC_{last}, and AUC_{inf}. [b]First time point collected in study SNBL.205.14 was at 8 hours postdose.

Repeat-dosing (Figure 6)

- KPL-716 3 mg/kg SC every 2 weeks allows for sufficient protection to serial IL-31 challenge at trough
- Weaker protection at trough manifests as increased variability

Figure 6. Repeated-dose KPL-716 SC inhibits pruritus from serial IL-31 challenge



Efficacious concentration defined via PK/PD correlation = 5 to 8.5 µg/mL. Scratching events are calculated as post–IL-31 challenge (3 µg/kg) minus pre–IL-31 challenge events. IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous.
*Statistically significant difference ($P<0.05$) from placebo, unpaired *t* test.

Safety

- There were no adverse effects or changes in body weight related to IL-31 or KPL-716 administration over the course of the study

CONCLUSIONS

- This model confirms target engagement and PD activity of KPL-716 in cynomolgus monkeys, which are homologous to humans for IL-31 and its receptor complex of IL-31Rα and OSMRβ[9]
- A single dose of KPL-716 10 mg/kg IV reduced the scratching response in primates for up to 4 weeks
- PK/PD correlation defined an efficacious concentration range of 5 to 8.5 µg/mL, at or above which KPL-716 protected cynomolgus monkeys from a supra-physiologic IL-31 challenge–induced pruritus
- Predictive modeling with single-dose IV PK/PD and single-dose SC PK was used to define repeated-dose SC regimens for further study
- Experimental results confirmed model-specified dosing regimens, with protection observed using 3 mg/kg SC every 2 weeks
- Consistent with these preclinical findings, single-dose KPL-716 IV reduced pruritus in human subjects with moderate to severe atopic dermatitis in a phase 1b clinical trial <<See Poster #560 for updated data>>
  - Reductions in pruritus were observed in the monotherapy period from week 1 through week 4 and through weeks 6–8 during coadministration of topical corticosteroids
- PK/PD modeling may support determination of practical chronic dose(s)/dosing intervals using an efficacious concentration derived from KPL-716 clinical trials

REFERENCES

1. Dillon SR, et al. *Nat Immunol*. 2004;5:752-60. **2.** Richards C. *ISRN Inflammation*. 2013;2013:1-23. **3.** Saleem MD, et al. *J Dermatol Treat*. 2017;28:591-9. **4.** Bilsborough J, et al. *J Allergy Clin Immunol*. 2006;117:418-25. **5.** Gangemi S, et al. *Allergy Asthma Proc*. 2017;38:401-8. **6.** Hermanns HM. *Cytokine Growth Factor Rev*. 2015;26:545-58. **7.** Mikhak Z, et al. Presented at: Congress of the European Academy of Dermatology and Venereology; September 12-16, 2018; Paris, France. **8.** Gonzales AJ, et al. *Vet Dermatol*. 2013;24:48-53.e11-42. **9.** Lewis KE, et al. *J Eur Acad Dermatol Venereol*. 2017;31:142-50.

ACKNOWLEDGMENTS

The authors acknowledge Wanchana Ungphakorn, Steve Choy, Eugene Lau, Fran Stringer, and Bruce Green of Model Answers Pty Ltd, Brisbane, Australia, for data analysis and modeling.

DISCLOSURES

This study is being sponsored by Kiniksa Pharmaceuticals, Ltd. Medical writing assistance was provided by Peloton Advantage, LLC, an OPEN Health company, funded by Kiniksa Pharmaceuticals, Ltd.

For an e-Print, scan this QR code. Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from the authors of this poster.