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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

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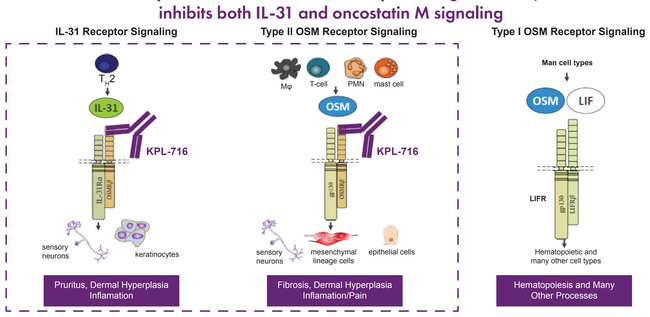
BACKGROUND

- 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

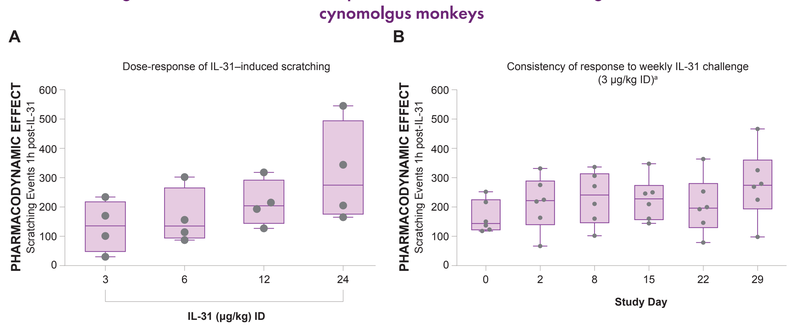
- Scratching events were reported as the number of events post–IL-31 challenge minus pre–IL-31 challenge

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

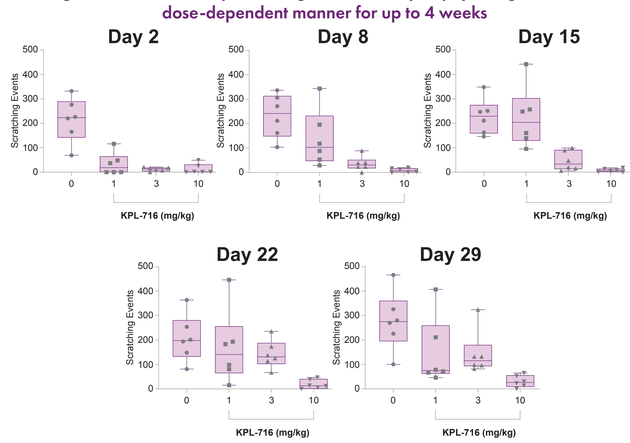


Events are calculated as post–IL-31 challenge minus pre–IL-31 challenge events. Boxes and whisker plots indicate data points for each animal in each dose group; the median is represented by a horizontal line within the box, and the box itself represents the interquartile range. ID, intradermal.
[a]Scratching 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

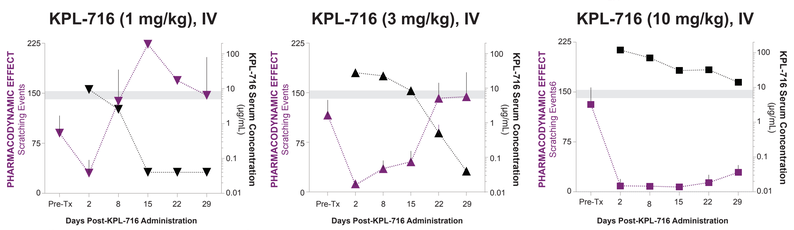


KPL-716 was administered intravenously (IV) on day 1.
Scratching events are calculated as post–IL-31 challenge minus pre–IL-31 challenge events. Boxes and whisker plots indicate data points for each animal in each dose group; the median is represented by a horizontal line within the box, and the box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

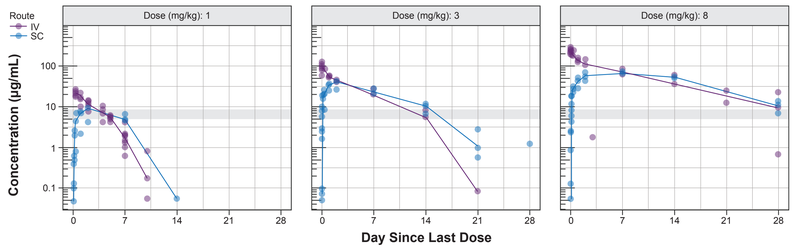
Days	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
G1 (0 mg/kg SC)	B	D	CB						DB		C					DB			C				DB				C			DB						C		D								
G2 (1 mg/kg SC)	B	D	CB						DB		C				C	DB			C				DB				C			DB						C		D								
G3 (2 mg/kg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

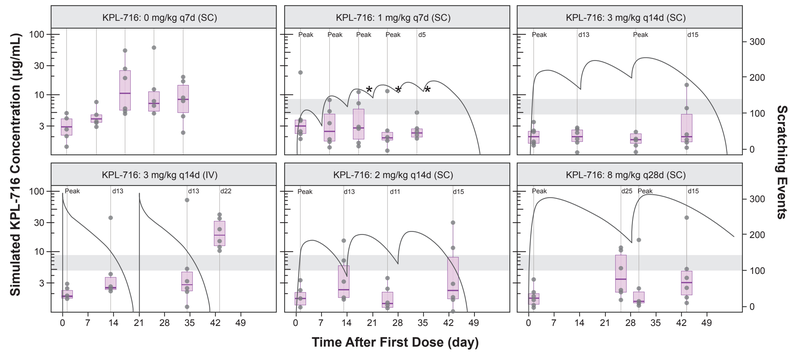
Dose (mg/kg)	Route	C_{max} (CV%) (µg/mL)	T_{max}[c] (hours)	AUC_{last} (CV%) µg•h/mL	AUC_{inf} (CV%) µg•h/mL	F
1	IV	19.73 (5.6)	8.01 (7.93-8.03)[b]	1569.63 (15.4)	1570.81 (15.4)	-
1	SC	6.77 (38.3)	72 (72-96)	1041.79 (33.5)	1044.01 (33.3)	0.66
3	IV	68.77 (1.9)	0.08 (0.08)	9353.62 (4.4)	9354.92 (4.4)	-
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

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DISCLOSURES

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