**BACKGROUND**

- Interleukin 31 (IL-31) signals through the heterodimeric complex consisting of IL-31 receptor alpha (IL-31Rα) and oncostatin M receptor beta (OSMRβ).
- IL-31 is produced by activated CD4+ T cells, primarily T helper cells, macrophages, and dendritic cells.
- IL-31 and its receptor complex induce pruritic skin disease, including atopic dermatitis and chronic urticaria.

**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 all ranges of 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.
- To determine the response of KPL-716 SC doses against IL-31–induced pruritus.
- To compare the efficacy of KPL-716 by subcutaneous (SC) and IV administration.

**RESULTS**

**Optimization of the model (Figure 2)**

- IL-31 induced 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/mL IL-31 dose was most variable; 3 μg/mL was chosen for subsequent experiments.

**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 10.
- KPL-716 10 mg/kg IV maintained an antipruritic effect through day 29.

**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.
- TMOD was estimated at 210 μg/mL.
- KPL-716 exposure increased with increasing dose.

**IV to SC bridge mini-PK**

- 16 animals were randomized to 4 SC dose groups: 3, 6, 12, and 24 μg/kg/3 w/kg in a weight-stratified manner.
- IL-31 (derived from Escherichia coli) was administered ID on day 1.

**METHODS**

**Optimization of the model**

- 8 animals were randomized to 4 SC dose groups: 3, 6, 12, and 24 μg/kg/3 w/kg in a weight-stratified manner.
- IL-31 (derived from Escherichia coli) 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, 4, 7 (after day 7), 15, 22, and 29.

**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.
- A single dose of KPL-716 10 mg/kg IV reduced the scratching response in primates for up to 4 weeks.
- KPL-716 protected cynomolgus monkeys from a supra-pharmacologic IL-31–challenge–induced pruritus.
- Predictive modeling with single IV PK/ID and single-dose SC PK was used to define repeated-dose SC regimen for further study.
- Experimental results confirmed model-specific dosing regimen, 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 A560 for updated data.”)
- Reductions in pruritus were observed in the monotherapy period from week 1 through week 4 and through weeks 6–8 during concomitant use of topical corticosteroids.
- PK/ID modeling may support determination of clinical doses/dosing intervals using an efficacious concentration derived from KPL-716 clinical trials.

**REFERENCES**


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**DISCLOSURES**

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