TITLE: KPL-716, an anti-oncostatin M receptor β (OSMRβ) monoclonal antibody, reduces IL-31-induced scratching behavior in cynomolgus monkeys: establishment and optimization of a PK/PD model

AUTHORS: Rohan Gandhi,[1] Karalyne Crowder,[2] Kory Barrow,[2] John F. Paolini[1]

[1]Kiniksa Pharmaceuticals Corporation, Lexington, Massachusetts, USA; [2]Altasciences Preclinical Seattle LLC, Everett, WA, USA

ABSTRACT

Interleukin (IL)-31 levels are elevated in skin and serum of patients with pruritic diseases. OSMRβ heterodimerizes with IL-31 receptor α or gp130 to form functional IL-31 and type II OSM receptors, respectively. KPL-716 targets OSMRβ and is a potential treatment for pruritic and fibrotic conditions. We optimized the dose of intradermal recombinant human IL-31, yielding a consistent, robust scratching response in cynomolgus monkeys and evaluated KPL-716 efficacy and PK/PD in this model. Scratching/grooming behavior was monitored with a Noldus Media Recorder pre- and post-IL-31 administration (3, 6, 12, or 24 µg/kg in 4 monkeys/group). IL-31 induced scratching in all animals and dose groups. Median (range) scratching events per IL-31 dose level were 135.5 (20-229), 130 (87-302), 204 (127-313), and 274.5 (169-541), respectively; 24-µg/kg was the most variable. Based on these responses, weekly IL-31 3 µg/kg was used to assess anti-pruritic effects of KPL-716 single IV dose (0, 1, 3, or 10 mg/kg, day 1) in 6 animals/group; IL-31 24 µg/kg was used as a legacy benchmark. KPL-716 attenuated scratching in a dose- and time-dependent manner. All KPL-716 dose levels reduced day 2 scratching events vs acclimation and control, an effect maintained at day 15 for KPL-716 3 mg/kg (median, 33; range, 5-99) and 10 mg/kg (median, 5.5; range, 0-18) and at day 29 for 10 mg/kg (median, 26.5; range, -9 to 65). The KPL-716 PK curve correlated with PD activity (minimally effective

plasma concentration range: 5.5-8.5 µg/mL). In summary, the cynomolgus monkey IL-31 challenge model was optimized with lower-dose IL-31, and KPL-716 exhibited dose- and time-dependent antipruritic effects that correlated with single-dose PK. Consistent with these preclinical findings, KPL-716 reduced pruritus in subjects with moderate to severe atopic dermatitis in a phase 1b clinical trial presented at EADV Meeting 2018.

KEYWORDS: Interleukins, pruritus, itch

DISCLOSURES:

This research was funded by Kiniksa Pharmaceuticals Corporation. RG and JFP are employees of Kiniksa Pharmaceuticals Corporation. KC and KB are paid consultants of Kiniksa Pharmaceuticals Corporation.