A Population Pharmacokinetic Model of KPL-716 in Healthy Volunteers and Patients with Atopic Dermatitis

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Background

- KPL-716, a fully human monoclonal antibody targeting oncostatin M receptor beta (OSMRβ), is under development for treatment of multiple chronic pruritic diseases such as prurigo nodularis (PN).

Aim

- The objectives of the analysis were to characterize the PK of KPL-716 following intravenous (IV) and subcutaneous (SC) administration in adult healthy volunteers (HV) and subjects with atopic dermatitis (AD).
- Investigate various SC dosing regimens to optimize practical chronic dosing in a target population.

Methods

- Single dose data from a Phase 1b clinical study in 57 HV and subjects with AD were included in the analysis.
- Most HV and AD subjects received weight-based IV administration (n=24, n=16, respectively; range: 0.3-20 mg/kg), followed by weight-based SC (n=6, n=4; 1.5 mg/kg) and fixed-dose SC (HV, n=7, 360 mg) administration.
- A non-linear mixed effects model was developed in NONMEM v7.3.
- Model diagnostics and visual predictive checks were used to evaluate the model.
- Simulations were performed using RxODE v0.6.3[1] to explore dosing regimens.

Conclusions

- A population model for KPL-716 was developed using data from primarily single-dose IV administration and limited single-dose SC data.
- The model was used to simulate future efficacy study dosing scenarios for chronic SC dose administration in patients with chronic pruritic diseases in which the target receptor may be up-regulated.
- The maximum deliverable SC weekly dose will support proof-of-concept studies, replicating exposures associated with a prior early signal of efficacy (single 7.5 mg/kg IV dose) and extending them into maintenance dosing.

References

1. Wang W et al. CPT Pharmacometrics Syst Pharmacol. 2016;5(1):3-10.
2. Levy G. Clin. Pharmacol. Ther. 1994;56:248-252.

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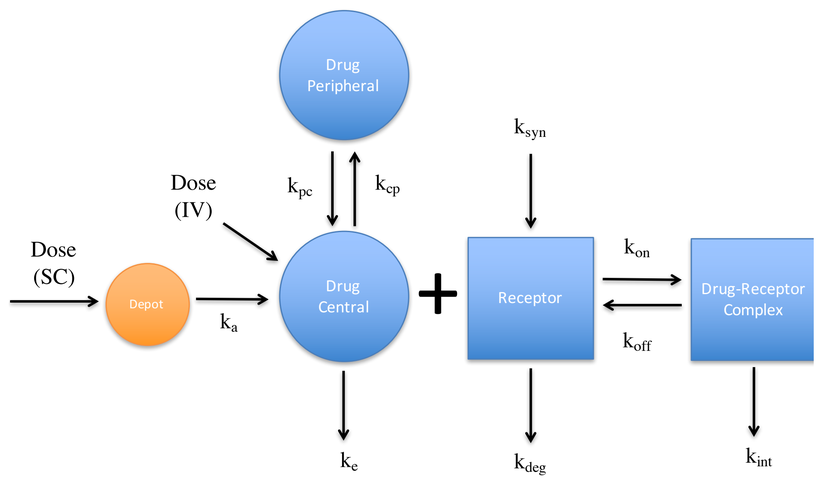
Population PK Model

- The PK of KPL-716 in HV and AD subjects following single-dose IV or SC administration was described using a target-mediated drug disposition (TMDD) model[2] to account for its non-linear clearance.
- Association (K_{on}) and dissociation (K_{off}) rate constants were determined experimentally at 0.734 $nM^{-1} \cdot h^{-1}$and 0.268 h^{-1}, respectively, and fixed during model development.
- Relative bioavailability of SC administration in AD was estimated for the model at 65% across the range of doses investigated (based on the comparison of PK of 1.5 mg/kg IV and SC in HV and AD subjects and then revised for dose-dependency based on PK of 360 mg SC in HVs).
- Body weight was included as a covariate on the central volume of distribution.

Model Schematic



Parameter Estimates for the Final Model

Parameter Description	Estimate (%RSE)
Central volume of distribution (V_c, L)	2.98 (5.7)
Covariate of weight on central volume	0.508 (37.2)
Antibody elimination rate constant (K_e, h^{-1})	0.00244 (13.5)
Central to peripheral distribution rate constant (K_{cp}, h^{-1})	0.00423 (19.7)
Peripheral to central distribution rate constant (K_{pc}, h^{-1})	0.00756 (12.9)
Absorption rate constant (K_a, day^{-1})	0.257 (25.5)
Relative bioavailability (%)	64.6 (11.1)
Baseline target expression level (HV) (R_0, nM)	0.290 (24.0)
Baseline target expression level (AD) (R_0, nM)	0.395 (9.9)
Complex internalization rate constant (K_{int}, h^{-1})	0.1 FIX†
Association rate constant (K_{on}, $nM^{-1} \cdot h^{-1}$)	0.7344 FIX‡
Dissociation rate constant (K_{off}, h^{-1})	0.267984 FIX‡
Target turnover rate constant (K_{deg}, h^{-1})	0.734 (5.8)
Between Subject variability for V_c	15.1 (15.7)
Between Subject variability for K_e	36.5 (19.1)
Between Subject variability for K_a	71.7 (38.3)
Residual unexplained variability (%)	16.9 (8.3)

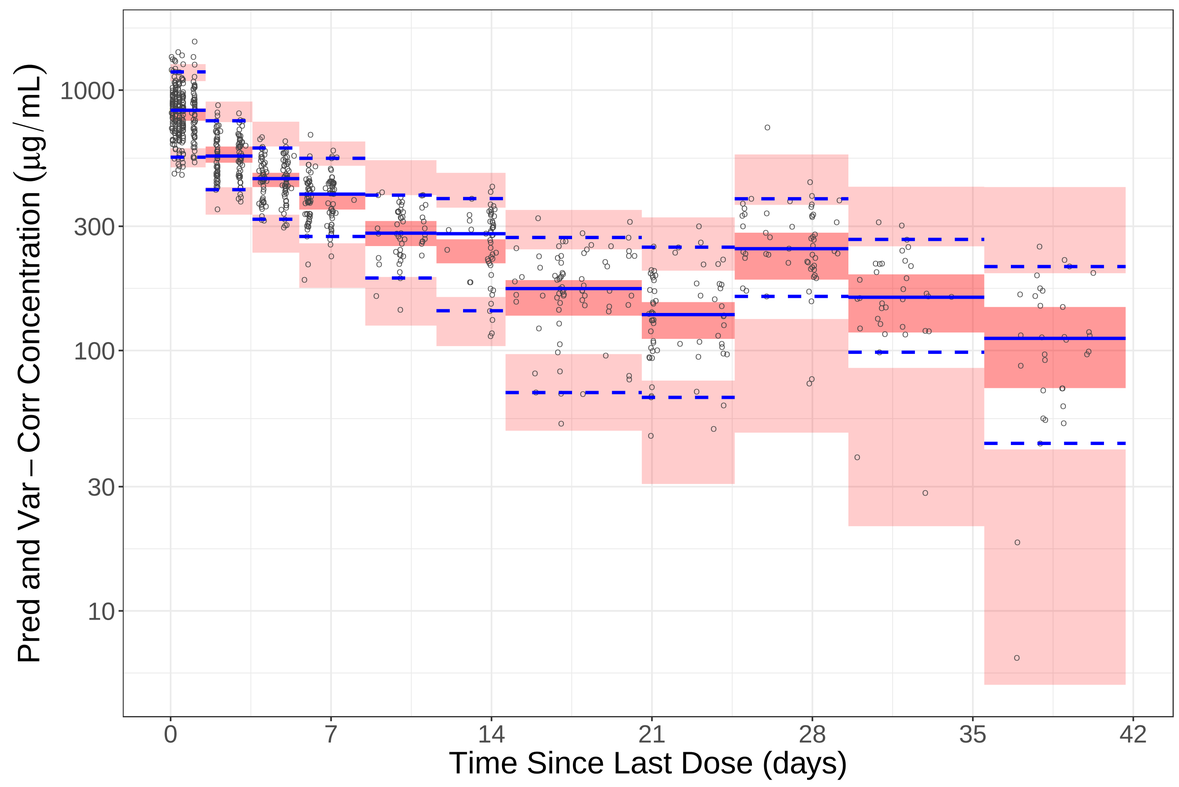
RSE = relative standard error.

V_C was modelled as follows: $V_C(L)=2.98 \cdot (\text{Weight (kg)}/79.9)^{0.508}$

† = Fixed to a low rate of internalisation for membrane bound targets.

‡ = Fixed to *in vitro* anti-OSMR monograph values.

Prediction and Variance Corrected Visual Predictive Check



Open circles = individual observed, dashed blue lines = observed 5th & 95th percentiles, solid blue line = observed median, shaded red areas = 90% prediction interval for the 5th, median, and 95th percentiles. Note: observations >42 days post-dose have been omitted from the plot to aid visualization.

Dosing Simulations

- A range of simulations was performed to evaluate various SC dosing regimens in subjects with AD assuming a maximum practical delivered dose of 360 mg KPL-716 (2mL SC injection).
- Exposure metrics and time to steady-state were derived for each simulated SC dosing regimen.
- The simulations were used to determine practical chronic dosing intervals using a C_{eff} derived from KPL-716 clinical trials.

Chronic Dosing Scenarios Simulation