

# NKTR-255 Exhibits Target Mediated Drug Disposition and Stimulates Proliferation of Cytotoxic Immune Cells in Cynomolgus Monkeys

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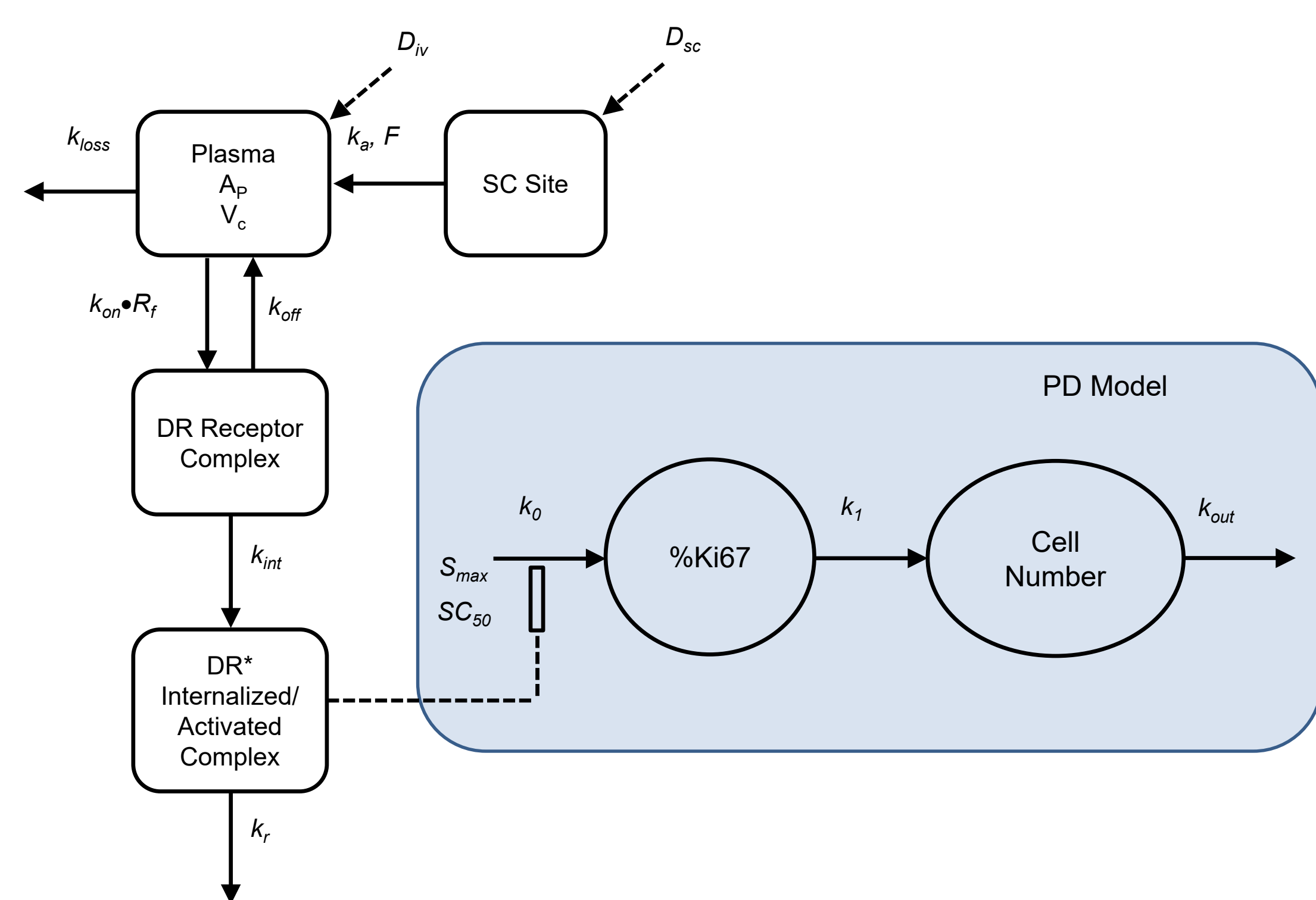
## Introduction

- IL-15 is a cytokine that activates T cells and NK cells and has long been recognized for its potential as an immunotherapeutic agent for the treatment of cancer.
- Exploiting this potential has been challenging due to unfavorable pharmacokinetic properties requiring daily dosing.
- NKTR-255 is a polymer-modified IL-15 that shows sustained exposure relative to hrIL-15 while retaining potency and high affinity for IL-15R $\alpha$ .
- Modeling was conducted to characterize the PK/PD of NKTR-255 in cynomolgus monkeys.

## Methods

- To assess the PK/PD effects in monkeys, NKTR-255 was administered via intravenous (iv) and subcutaneous (sc) routes and whole blood was collected at specific time points.
- PK data was collected after seven iv doses ranging from 0.001-0.3 mg/kg and three sc doses ranging from 0.01-0.1 mg/kg. All NKTR-255 doses are expressed in IL-15 equivalents.
- NKTR-255 was quantified using ELISA-based plasma measurement.
- Flow cytometry was used to measure signaling proliferative status (Ki-67 expression) and absolute frequency of various lymphocyte subpopulations.
- Modeling was conducted using NONMEM 7; and first-order conditional estimation method with interaction (FOCEI) was implemented for all runs.

Schematic Representation of TMDD PK Model and Indirect-Response PD Model (Mager et al, 2003) for NKTR-255 Following IV and SC Administration



Equations Describing Target Mediated Drug Disposition (TMDD) PK Model and Indirect-Response Pharmacodynamics (PD) Model (Mager et al, 2003) for NKTR-255 Following IV and SC Administration

- $\frac{dA_{p,iv}}{dt} = k_{off} \cdot DR_{iv} - \left(\frac{k_{on}}{V_c}\right) \cdot A_{p,iv} \cdot R_{f,iv} - k_{loss} \cdot A_{p,iv}, IC = IV \text{ Dose}$  Eq.(1)
- $\frac{dA_{p,sc}}{dt} = k_a \cdot A_{sc} + k_{off} \cdot DR_{sc} - \left(\frac{k_{on}}{V_c}\right) \cdot A_{p,sc} \cdot R_{f,sc} - k_{loss} \cdot A_{p,sc}$  Eq.(2)
- $\frac{dDR_{ad}}{dt} = \left(\frac{k_{on}}{V_c}\right) \cdot A_{p,ad} \cdot R_{f,ad} - (k_{off} + k_{int}) \cdot DR_{ad}$  Eq.(3)
- $\frac{dA_{sc}}{dt} = -k_a \cdot A_{sc}, IC = F \cdot SC \text{ Dose}$  Eq.(4)
- $R_{f,ad} = R_{max} - DR_{ad}$  Eq.(5)
- $\frac{dDR_{ad}}{dt} = k_{int} \cdot DR_{ad} - k_r \cdot DR_{ad}^*$  Eq.(6)
- $\frac{dKi_{67}}{dt} = k_0 \cdot \left(1 + \frac{S_{max} \cdot DR_{ad}^*}{SC_{50} + DR_{ad}^*}\right) - k_1 \cdot Ki_{67}$  Eq.(7)
- $\frac{dCN}{dt} = k_1 \cdot Ki_{67} - k_{out} \cdot CN$  Eq.(8)
- $k_0 = CN^0 \cdot k_{out}$  Eq.(9)
- $Ki_{67}^0 = \frac{k_0}{k_1}$  Eq.(10)
- $S_{max} = \frac{E_{max}}{Ki_{67}^0} - 1$  Eq.(11)

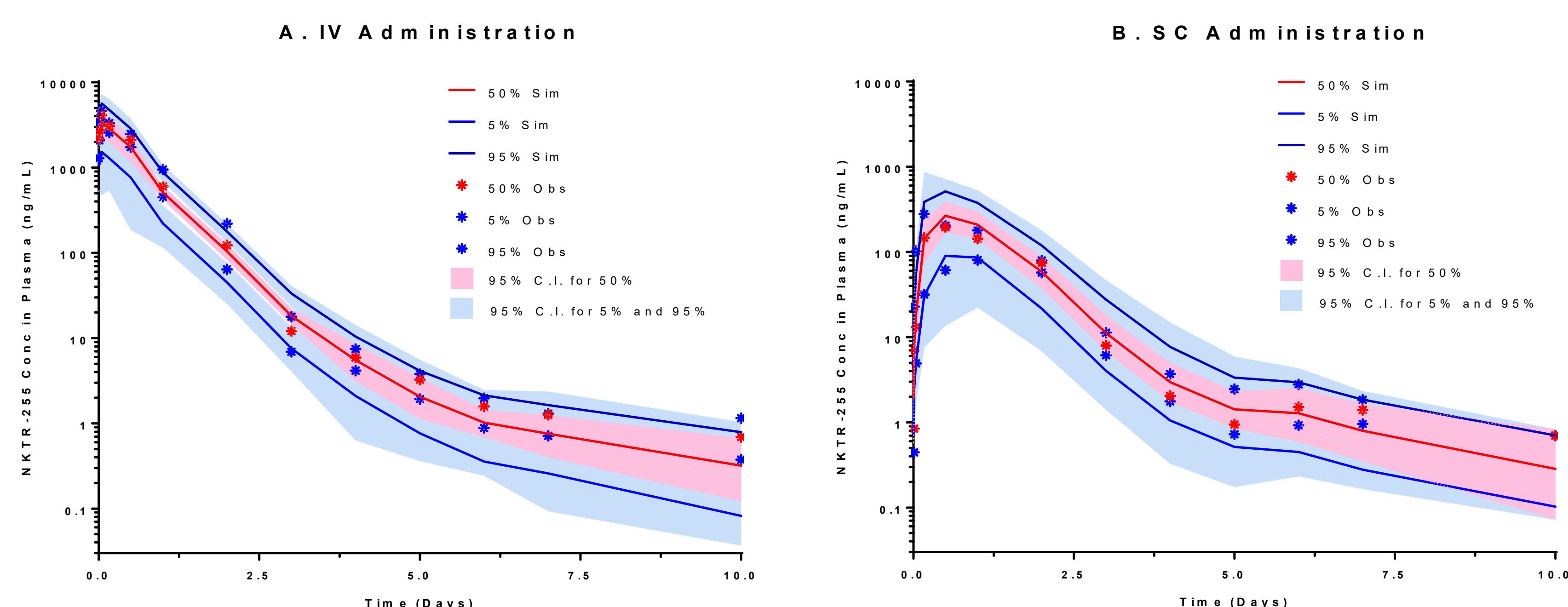
Abbreviations:  $A_p, V_c$ : amount of drug and volume of central compartment;  $D_{iv}$  and  $D_{sc}$ : doses for iv and sc administration (ad) routes;  $k_{on}, k_{off}, k_{int}$ : association, dissociation, internalization rate constants;  $k_{loss}$ : additional drug elimination pathways;  $k_a$ : absorption from sc dosing site to the central compartment; iv and sc: intravenous and subcutaneous administration (ad) routes;  $R_{max}$ : maximum receptor quantity;  $R_f$ : amount of free cell-surface receptors;  $DR_{ad}$ : drug-receptor complex;  $F$ : bioavailability;  $DR_{ad}^*$ : internalized/activated drug-receptor complex;  $k_r$ : loss of  $DR^*$ ;  $k_0$ : zero-order input rate for Ki-67;  $k_1$ : first-order loss rate for Ki-67 which also represents the input rate for cells;  $k_{out}$ : first-order loss rate for cells;  $Ki_{67}^0$ : %Ki-67;  $CN$ : Number of cells (CD8 T-cells and NK cells);  $S_{max}$ : maximum stimulation effect by drug;  $SC_{50}$ : drug concentration at 50% of maximum effect;  $E_{max}$ : maximum PD response for %Ki-67;  $Ki_{67}^0, CN^0$ : baseline values for %Ki-67 and cell numbers, respectively

## Results (Executive Summary)

- PK parameter estimates for elimination of NKTR-255 from central compartment ( $k_{loss}$ ), receptor binding ( $k_{on}$  and  $k_{off}$ ) and internalization ( $k_{int}$ ) rates are 0.0641 hr $^{-1}$ , 1.25 nM $^{-1}$ hr $^{-1}$ , 0.136 hr $^{-1}$ , and 0.0094 hr $^{-1}$ , respectively.
- PD parameter estimates were independent of dosing route and shows that NKTR-255 stimulates proliferation of NK cells more potently than CD8 T cells by a factor of ~10-fold with potency ( $SC_{50}$ ) of 0.0252 nmol/kg and 0.24 nmol/kg, respectively, in cynomolgus monkeys.

## Results

Prediction-Corrected Visual Predictive Check Plots for NKTR-255 PK Following: A) IV and B) SC Administration in Monkeys

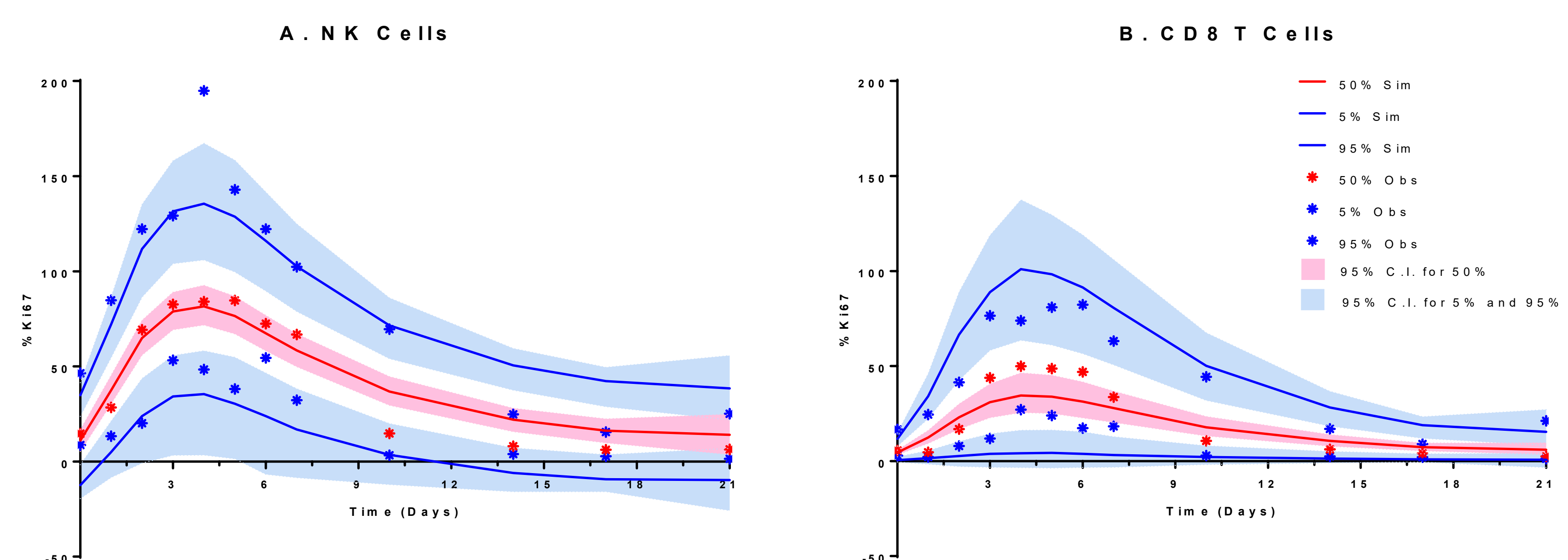


PK Parameter Estimates Following IV and SC Administration of NKTR-255 in Monkeys

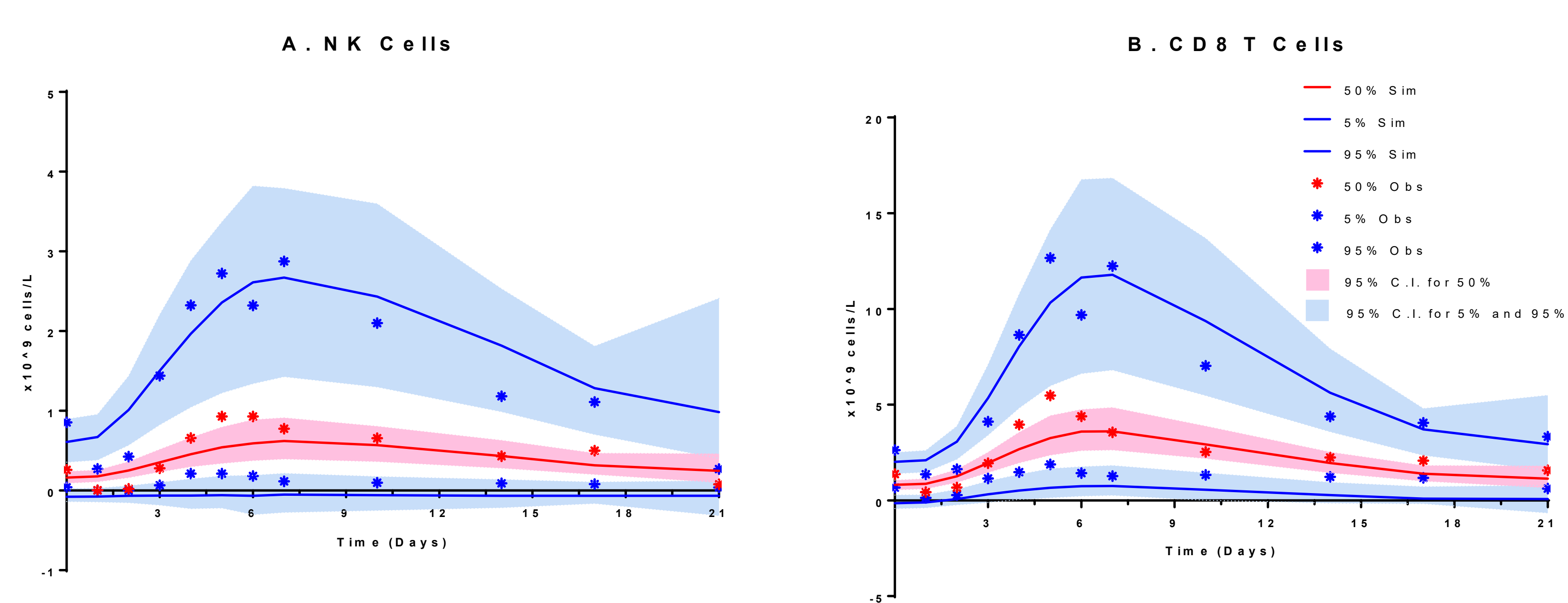
PK Parameter (units)	Estimate	%RSE (of Estimate)	IIV	%RSE (of IIV)
$k_{loss}$ (hr $^{-1}$ )	0.0641	2	--	--
$k_{on}$ (nM $^{-1}$ hr $^{-1}$ )	1.25	25	--	--
$k_{off}$ (hr $^{-1}$ )	0.136	13	--	--
$k_{int}$ (hr $^{-1}$ )	0.0094	17	0.168	54
$R_{max}$ (nmol/kg)	0.196	17	--	--
$V_c$ (mL/kg)	37	4	--	--
$k_a$ (hr $^{-1}$ )	0.0988	15	0.148	47
$F$	0.657	14	0.0906	60
Proportional error constant	0.117	10	--	--

$k_{loss}$ : additional drug elimination pathways;  $k_{on}, k_{off}, k_{int}$ : association, dissociation, internalization rate constants;  $R_{max}$ : maximum receptor quantity;  $V_c$ : volume of central compartment;  $k_a$ : absorption from sc dosing site to the central compartment;  $F$ : bioavailability; IIV: inter-individual variability; RSE: relative standard error

Prediction-Corrected Visual Predictive Check Plots for NKTR-255 PD for %Ki-67 for: A) NK and B) CD-8 T Cells



Prediction-Corrected Visual Predictive Check Plots for NKTR-255 PD for Number of Cells for: A) NK and B) CD-8 T Cells



PD Parameter Estimates Following IV and SC Administration of NKTR-255 in Monkeys

PD Parameter (units)	NK Cells		CD8 T Cells	
	Estimate (%RSE)	IIV (%RSE)	Estimate (%RSE)	IIV (%RSE)
$k_r$ (hr $^{-1}$ )	0.0425 (6)	--	0.0192 (21)	0.3 (44)
$E_{max}$ (%)	100 (fix)	0.00593 (66)	100 (fix)	0.0366 (115)
$SC_{50}$ (nmol/kg)	0.0252 (14)	0.0816 (61)	0.24 (22)	--
$Ki_{67}^0$ (%)	18.8 (6)	--	6.1 (16)	0.114 (56)
$k_1$ (hr $^{-1}$ )	0.0313 (8)	--	0.018 (16)	--
$CN^0$ (x10 $^9$ cells/L)	0.178 (18)	0.596 (23)	0.648 (19)	0.139 (62)
Proportional error constant	--	--	0.574 (4)	--
Additive error (%)	16.8 (5)	--	--	--
Proportional error constant	0.65 (8)	--	0.321 (18)	--
Additive error (x10 $^9$ cells/L)	0.156 (18)	--	0.706 (28)	--

$k_r$ : loss of  $DR^*$ ;  $E_{max}$ : maximum PD response for %Ki-67;  $SC_{50}$ : drug concentration at 50% of maximum effect;  $k_1$ : first-order loss rate for %Ki-67;  $Ki_{67}^0, CN^0$ : baseline values for %Ki-67 and cell numbers, respectively

## Conclusions

- NKTR-255 displays TMDD PK disposition. Similarly to hrIL-15, NKTR-255 stimulates the proliferation of NK cells more potently than the CD8 T-cells in cynomolgus monkeys.
- The model parameters along with the in-vitro potency values will be used to predict MABEL dose selection in first-in-man clinical studies.