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Quantitative Prediction of Human Pharmacokinetics for Duvortuxizumab from Cynomolgus Monkey Data: A Translational Pharmacokinetic Modeling Approach

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INTRODUCTION

- CD19, a pan B-cell marker, is a promising target for the treatment of B-cell malignancies because of its expression on most B-cell lymphomas and leukemias.[1]
- Duvortuxizumab, also known as JNJ-64052781 and MGD011, is a Fc-bearing bispecific CD19 x CD3 DART® protein which contains binding domains for CD19 and CD3 antigens.
- Duvortuxizumab was designed to target CD19$^+$ cells for recognition and elimination by CD3-expressing T-lymphocytes.[2]
- A first-in-human (FIH), phase 1 dose-escalation trial of duvortuxizumab in patients with relapsed or refractory B-cell malignancies is ongoing (ClinicalTrials.gov NCT02454270).
- Here we report the results from a translational pharmacokinetic (PK) model that utilized duvortuxizumab PK data from cynomolgus monkeys to predict duvortuxizumab PK in humans.

METHODS

PK Studies in Cynomolgus Monkeys

Study 1

- Two groups of cynomolgus monkeys (n=2/sex/group) were administered 4 intravenous (2-hr IV) doses of duvortuxizumab once weekly at intra-animal escalating doses of 0.5, 5, and 50 (2x) µg/kg or 2, 10, and 100 (2x) µg/kg.
- Four groups of cynomolgus monkeys (n=1/sex/group) were administered 3 repeat doses of duvortuxizumab at 0.005 µg/kg, 0.05 µg/kg, or 0.5 µg/kg once weekly or 5 repeat doses at 0.5 µg/kg every 3 to 4 days by 2-hr IV infusion.
  - Serum concentrations above the lower limit of quantification were obtained at dose levels >0.5 µg/kg.

Study 2

- Four groups of cynomolgus monkeys (n=5/sex/group) were administered 2-hr IV infusions of duvortuxizumab at 0.2, 2, 5, or 10 µg/kg once weekly for 4 weeks.

Translational PK Modeling

- PK parameters were obtained by 2-compartmental modeling using pooled data (N=51) from studies 1 (n=12) and 2 (n=39).
- The mean values of PK parameters from all animals pooled across both studies were used for interspecies scaling.
- The general form of the interspecies scaling equation was $Y=a*W^b$, where Y is the PK parameter, W is body weight, a is a proportionality constant, and b is the allometric exponent.
  - Allometric exponents of 0.75 and 1.0 were used for clearance (CL) and volume of distribution (V), respectively.
  - Assuming a body weight of 3 kg for a cynomolgus monkey and 70 kg for a human, CL in monkeys was divided by 2.2 to arrive at the estimated CL in humans.
- WinNonlin (Phoenix WinNonlin 6.3) was used to simulate expected profiles in humans.

RESULTS

PK in Cynomolgus Monkeys

- Duvortuxizumab was reasonably characterized using a 2-compartment model with linear CL from the central compartment.
- PK parameters from the pooled studies are presented in **Table 1**.

Table 1. Pooled PK Parameters Derived from 2-Compartmental Modeling of Duvortuxizumab in Cynomolgus Monkeys

Pooled Studies (N=51)	Dose Range (µg/kg)	CL (mL/h/kg)	CLD_2 (mL/h/kg)	V_1 (mL/kg)	V_2 (mL/kg)	MRT (h)	$t_{1/2,\beta}$ (h)
Mean	0.2 to 100	0.797	2.29	51.7	88.8	190.6	161.4
SD		0.198	2.50	6.6	30.1	74.0	61.3

CL = clearance; CLD_2 = intercompartmental clearance; MRT = mean residence time; N = number of animals; PK = pharmacokinetic; SD = standard deviation; $t_{1/2,\beta}$ = mean beta half-life; V_1 = volume of distribution for the central compartment; V_2 = volume of distribution for the peripheral compartment.

Predicted Human PK

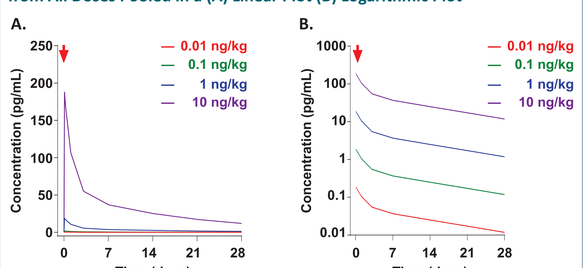
- Duvortuxizumab PK parameters were estimated in humans assuming a single IV infusion administered over 2 hrs (**Table 2**).
- Estimated human PK parameters were used to simulate serum concentration-time profiles for human doses ranging from 0.01 to 10 ng/kg (**Figure 1**).

Table 2. Predicted PK Parameters in Humans for Duvortuxizumab Administered as a Single 2-hr IV Infusion

	Dose (ng/kg)	C_{max} (pg/mL)	AUC (pg/mL·h)	CL (mL/h/kg)	CLD_2 (mL/h/kg)	V_1 (mL/kg)	V_2 (mL/kg)	MRT (h)	$t_{1/2,\beta}$ (h)
Pooled studies (all doses)	0.01	0.188	28	0.362	1.04	51.7	88.8	405	495
	0.1	1.88	276						
	1	18.8	2762						
	10	188	27624						

AUC = area under the plasma concentration-time curve; CL = clearance; CLD_2 = intercompartmental clearance; Cmax = maximum plasma concentration; IV = intravenous; MRT = mean residence time; PK = pharmacokinetic; $t_{1/2,\beta}$ = mean beta half-life; V_1 = volume of distribution for the central compartment; V_2 = volume of distribution for the peripheral compartment.

Figure 1. Predicted Human Serum Concentration-Time Profiles of Duvortuxizumab Scaled from Cynomolgus Monkey PK Parameter Values from All Doses Pooled in a (A) Linear Plot (B) Logarithmic Plot



CONCLUSIONS

- PK of duvortuxizumab in cynomolgus monkeys was reasonably characterized using a 2-compartment model with linear CL from the central compartment.
- The translational PK model has been used to aid dose escalation of duvortuxizumab in the ongoing FIH, phase 1 trial.
- This work showcases the potential of translational PK modeling in supporting the selection of a FIH dose escalation strategy utilizing preclinical PK information.

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