

Translational PK/PD modelling and prediction of an efficacious human dose of DNDI-6148 for the treatment of cutaneous leishmaniasis

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1 INTRODUCTION

- Cutaneous leishmaniasis is the most common manifestation of the parasitic neglected tropical disease leishmaniasis¹.
- Current treatment options for cutaneous leishmaniasis are antiquated, toxic, have suboptimal efficacy, and **lack oral options**².
- There is a need to evaluate the **translational value of animal models of cutaneous leishmaniasis** to inform human dose selection in clinical trials.

2 OBJECTIVES

- The objective was to characterize the target-site PK/PD of drug candidate DNDI-6148 in a murine *L. major* model, scale preclinical PK to humans, and predict a human efficacious dose based on the established exposure–response relationship.

4 RESULTS

- DNDI-6148 PK in mice was described by a one-compartment model with dose-dependent bioavailability, saturable clearance, and a skin-to-plasma ratio of 0.56 for both infected and non-infected skin.
- Parasite clearance at the infection site followed a sigmoidal E_{max} relationship, driven by free skin concentrations (fEC₅₀: 165 µg/L [95% CI: 121–208]).

Figure 1. Structure of DNDI-6148 PK/PD model

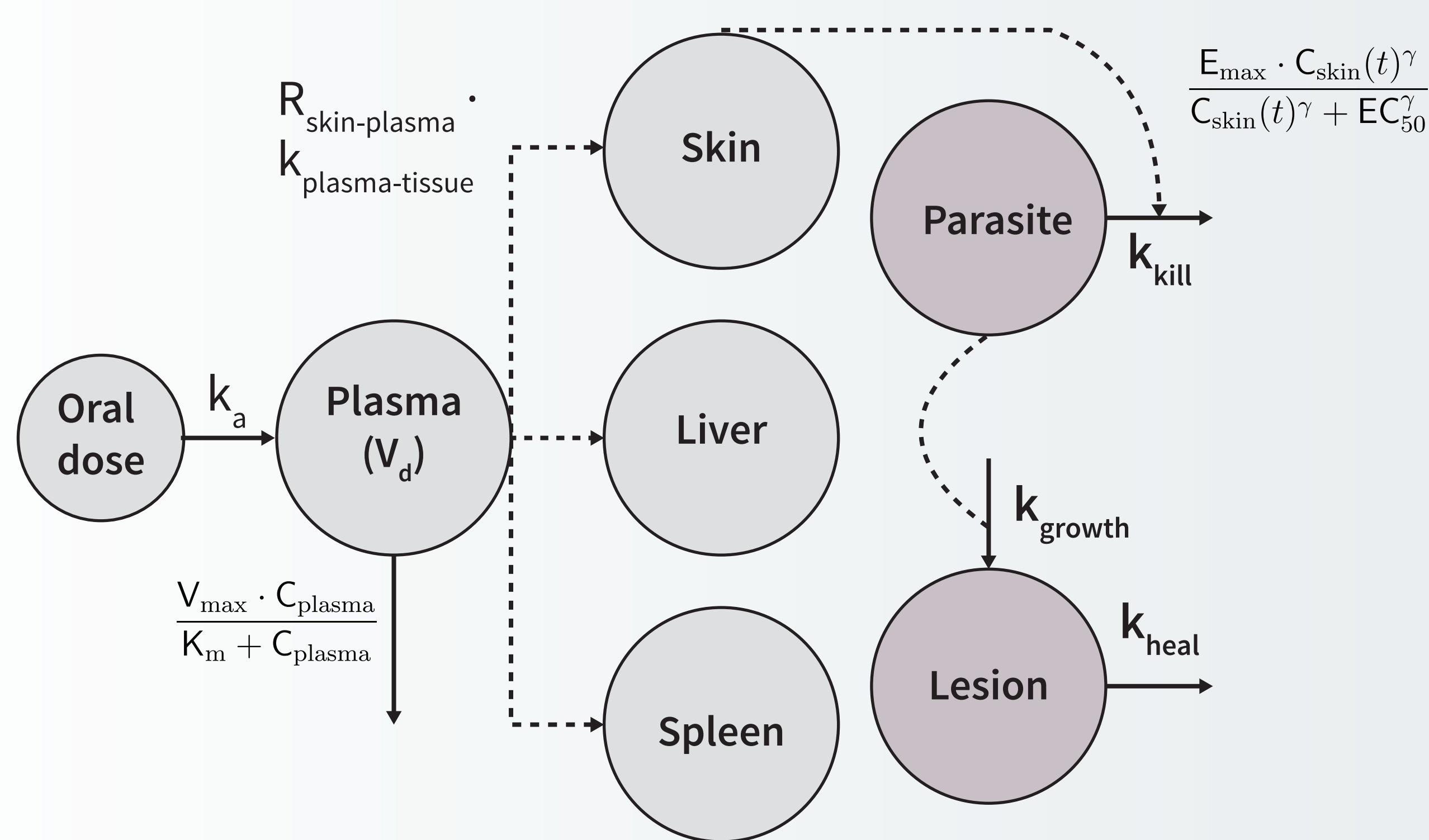


Table 1. Selected PK/PD model parameters

Parameter	Unit	Estimate [IIV]
R _{skin-plasma}	-	0.56 [37%]
R _{liver-plasma}	-	1.9 [30%]
R _{spleen-plasma}	-	0.34 [44%]
Parasite _{base}	log ₁₀ photons/s	8.0 [60%]
E _{max}	hr ⁻¹	0.049
fEC ₅₀	µg/L	165
Lesion _{base}	mm ²	31 [35%]
slope	2.78 · 10 ⁻⁴ /photons	0.0029
k _{heal}	hr ⁻¹	0.027

3 METHODS

- PK/PD data were collected from 30 BALB/c mice infected in the rump with luciferase-expressing *L. major* promastigotes.
- Mice were evenly distributed across five oral dosage groups (control, 6.25, 12.5, 25, and 50 mg/kg), and treated with DNDI-6148 BID for 10 consecutive days.
- Plasma PK samples were collected at 0.5, 1, 2, 4, 8, and 24 hours on days 1 and 10. Tissue samples (infected skin, non-infected skin, liver, spleen) were collected at end of treatment (day 10). Parasite load was quantified by bioluminescent imaging on days 0, 1, 2, 3, 5, 7, and 9; lesion size was measured daily from day 1 to 10.



- Human PK parameters were predicted from three preclinical species (mouse, rat, and dog) using allometric scaling.
- Predicted human PK parameters were combined with tissue distribution characteristics and PD components from the murine PK/PD model. The probability of target attainment for 95% and 99% parasite reduction from baseline in humans was determined by simulating 10,000 human PK/PD profiles. Simulations were performed for 70-kg adults with a dose range of 3–27 mg/kg for 7–14 days, administered once daily, in increments of 1.0 mg/kg.

Figure 2. VPC parasite bioluminescence in mice

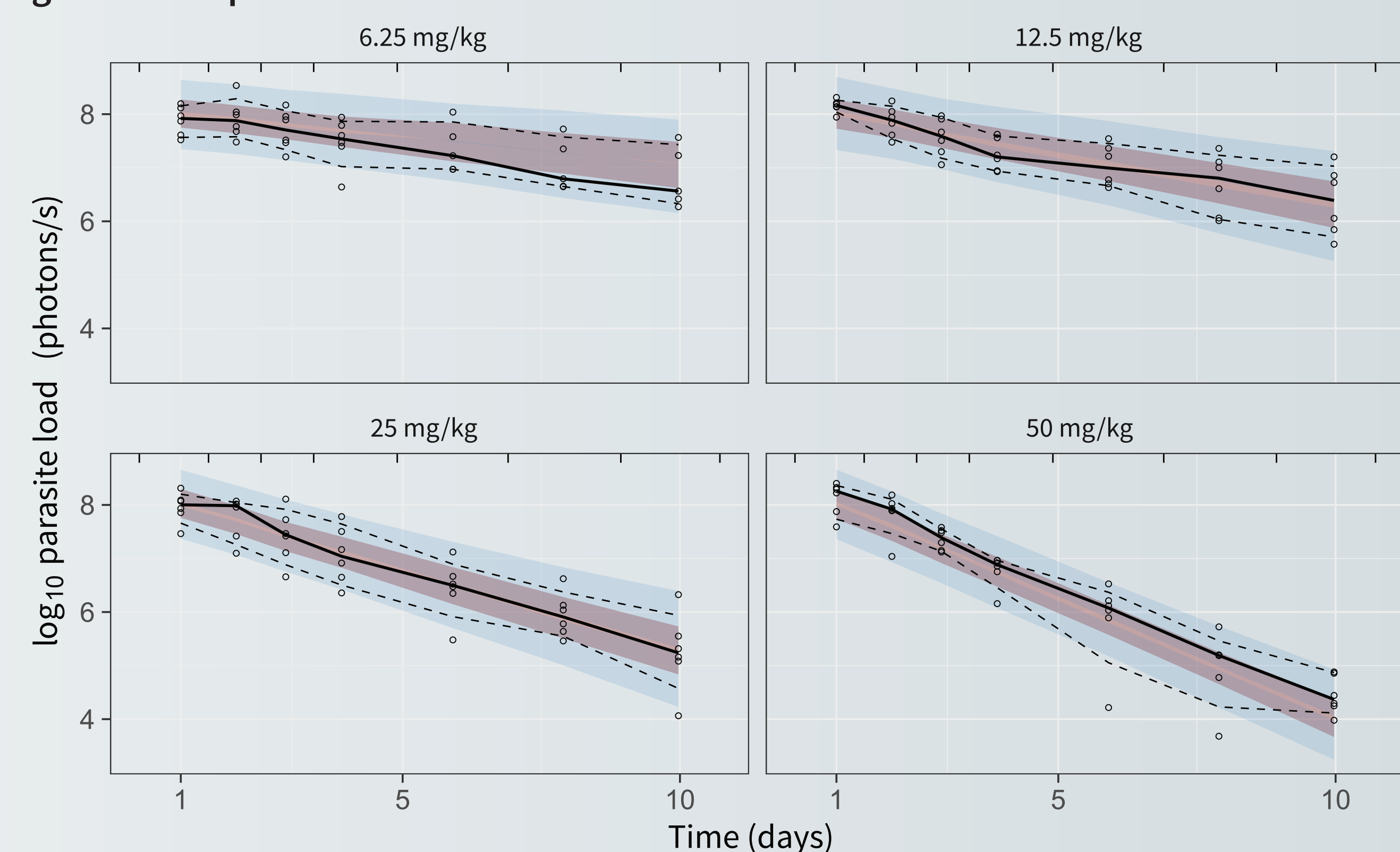
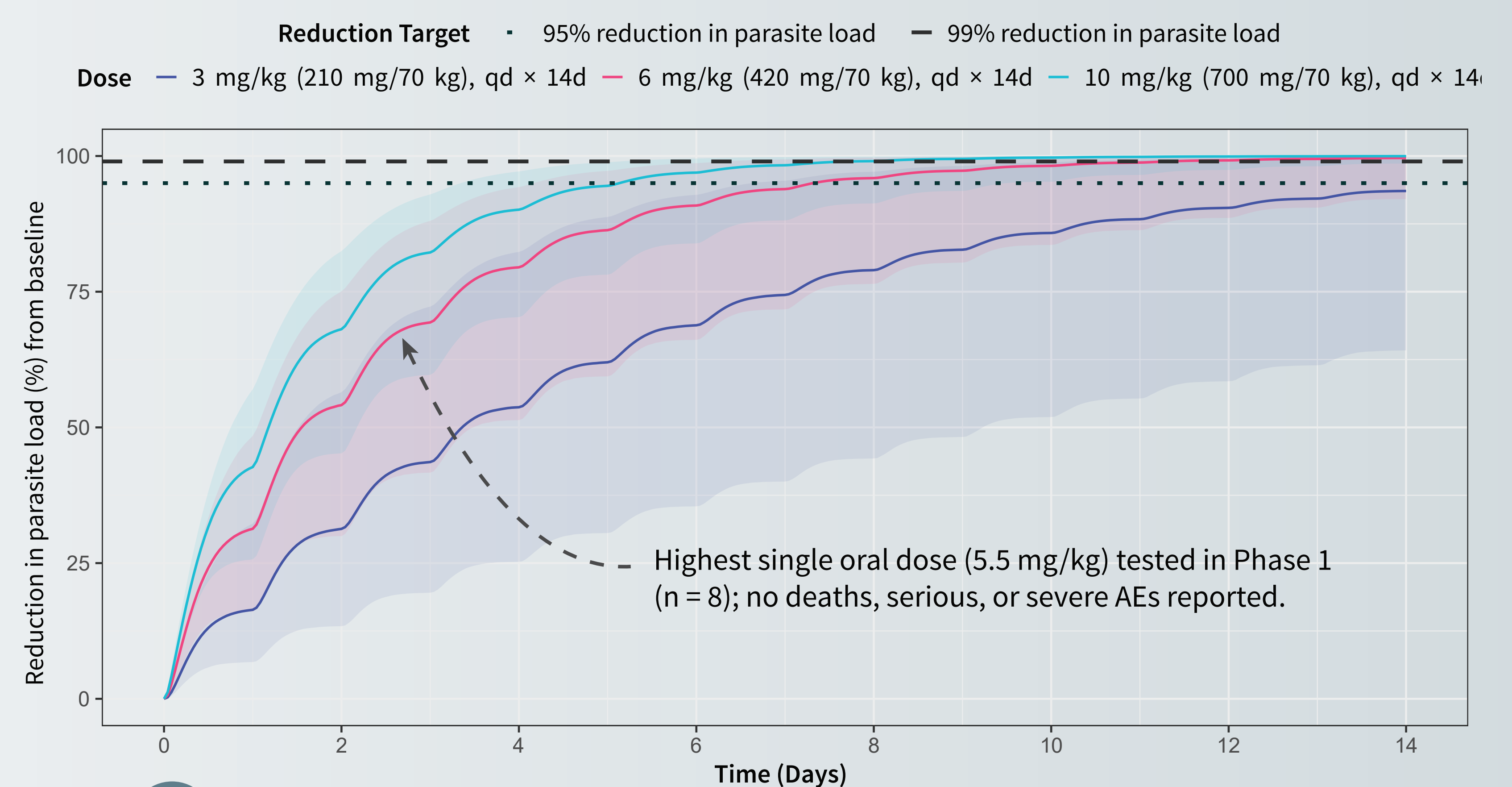


Figure 3. Model-predicted parasite reduction in humans



5 CONCLUSIONS

- Dose regimens of 6.0 and 10 mg/kg qd DNDI-6148 for 14 days were predicted to be sufficient to achieve 95% and 99% parasite reduction from baseline in >90% of the simulated human profiles
- Predicted human AUCs at 6–10 mg/kg/day are below NOAEL exposures in cynomolgus monkeys