

Preclinical population pharmacokinetic modelling of skin target site exposure of DNDI-o690 and DNDI-6148 in the treatment of cutaneous leishmaniasis

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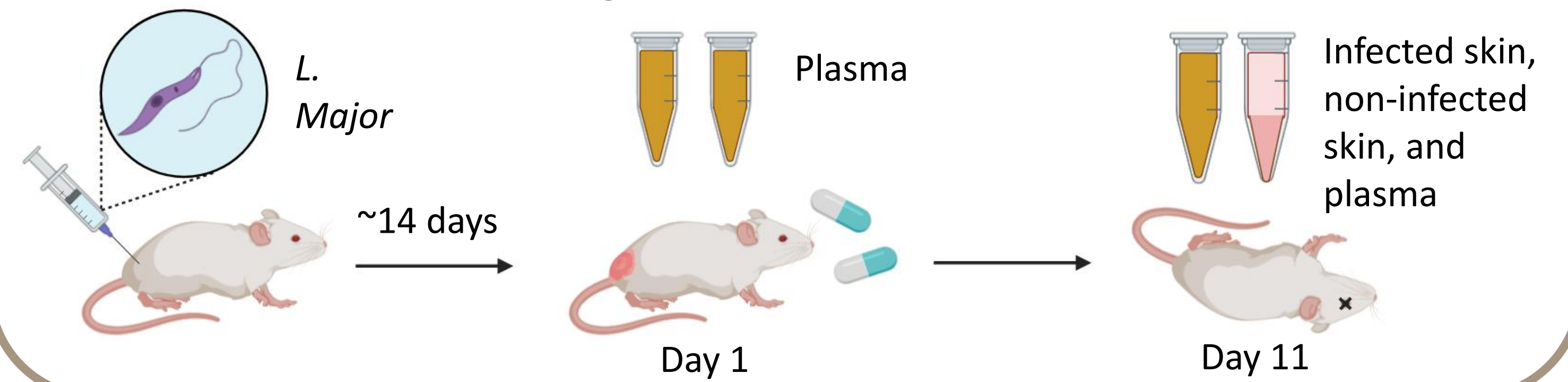
Introduction & Objectives

- Cutaneous Leishmaniasis represents the most common disease manifestation of the neglected tropical disease leishmaniasis, caused by various species of the protozoan parasite genus *Leishmania*.
- Despite potentially causing lifelong scarring, serious disability and social stigmatization, current treatment options are associated with severe limitations in terms of safety, efficacy and/or cost.
- Drugs for Neglected Disease initiative (DNDi) has identified two compounds, nitroimidazole DNDI-o690 and benzoxaborole DNDI-6148, as promising lead candidates, demonstrating excellent anti-leishmanial activity in various in vitro and in vivo CL models, but little is known about their distribution into the skin target site.

Aim: characterize the murine plasma population pharmacokinetics of two novel anti-leishmaniasis drug candidates, DNDI-o690 and DNDI-6148, and to explore target site exposure in the skin.

Methods

- 24 L. major infected BALB/c mice were included in each study, divided equally among four dosage groups (6.25 mg/kg, 12.5 mg/kg, 25 mg/kg, and 50 mg/kg) and orally administered DNDI-o690 (QD) or DNDI-6148 (BID) for 10 consecutive days.
- Plasma PK samples for DNDI-6148 were collected at 0.5, 1, 2, 4, 8, and 24 hours, and for DNDI-o690 at 0.5, 1, 2, 4, 8, 12, and 24 hours, on both day 1 and day 10. Infected and non-infected skin samples were collected 24 hours post-dose on day 10.
- PPK characterized using MonolixSuite2023R1 and NONMEM 7.5.



Results

Table 1. Selected population plasma PK parameters for DNDI-6148

Parameters	Estimate (%RSE)	SIR 95% CI
Absorption rate constant (k_a) [1/hr]	2.66 (19.5)	1.98 – 3.99
Volume of distribution central compartment (V/F) [L] ^a	0.0245 (6.3)	0.022 – 0.028
Maximum elimination rate (V_m) [μ g/hr] ^a	65.4 (11.2)	53.3 – 82.2
Michaelis-Menten constant (K_m) [μ g/L]	8000 (12.9)	6237 – 10396
Effect of dose on F (power function ^b)	-0.338 (10.7)	-0.41 – -0.27

^aAllometric scaled based weight with power exponent of 0.75 for clearance and 1 for volume of distribution. Estimate is given for a standardized weight of 22 g. ^bF · (dose/dose)⁰

Figure 1. Simulation of skin exposure of DNDI-6148 at different dose levels

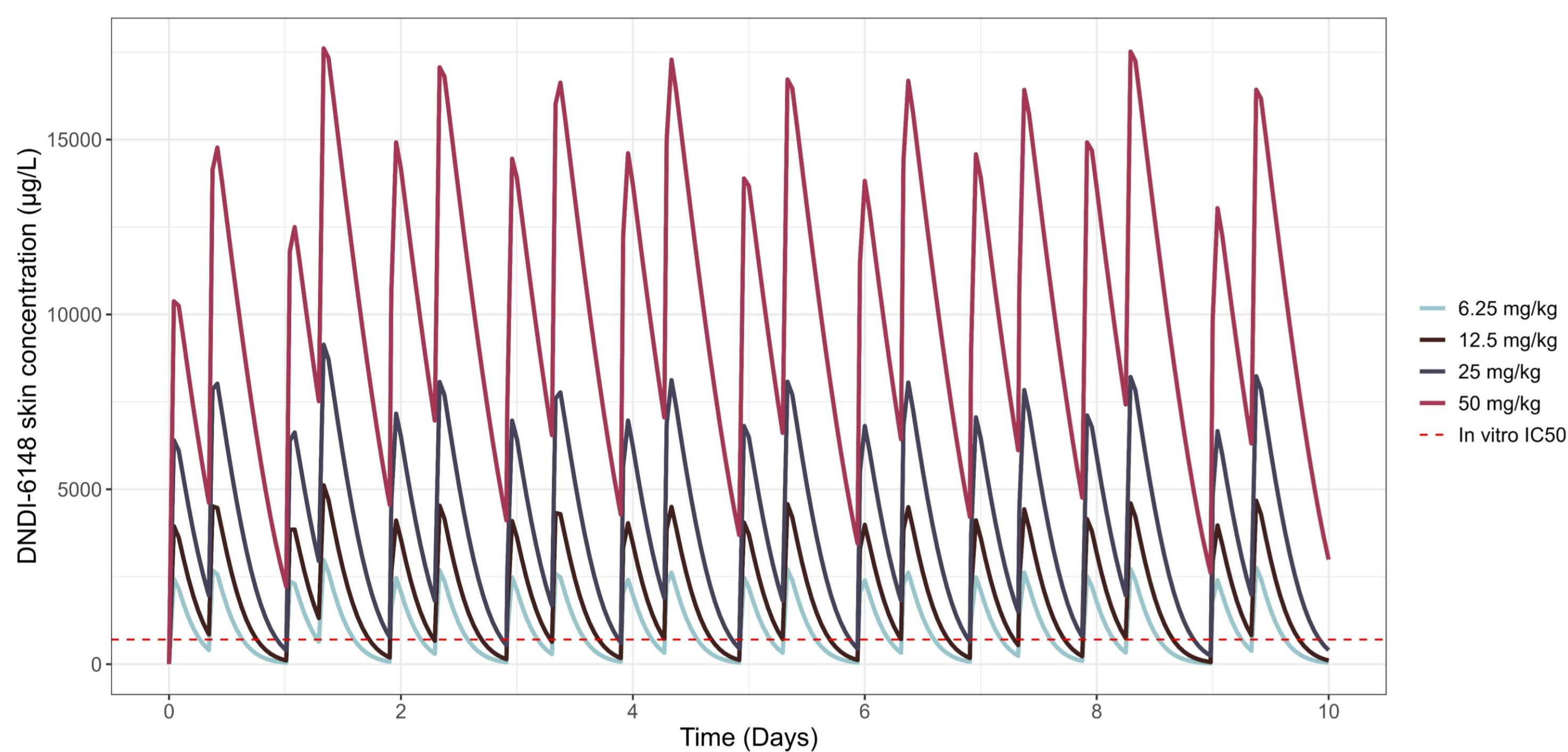


Table 3. Skin target site penetration of DNDI-6148 and DNDI-o690

Parameter [IIV %CV]	DNDI-6148	DNDI-o690
Infected skin to plasma ratio ($R_{\text{infskin:pl}}$)	0.54	0.21
Non-infected skin to plasma ratio ($R_{\text{non-infskin:pl}}$)	[IIV 37%]	0.16
Intercompartment rate transfer of drug from the plasma to skin ($k_{p:s}$) fixed to near-instantaneous value.		

Table 2. Selected population plasma PK parameters for DNDI-o690

Parameters	Estimate (%RSE)	FIM 95% CI
First absorption rate constant (k_{a1}) [1/hr]	2.34 (11.9)	1.86 – 2.94
Second absorption rate constant (k_{a2}) [1/hr]	0.40 (23.3)	0.20 – 0.78
Volume of distribution central compartment (V/F) [L] ^a	0.015 (13.5)	0.012 – 0.020
Clearance (CL/F) [L/hr] ^a	0.002 (12.9)	0.0016 – 0.0024
Fraction of dose for k_{a1} (F_1)	0.60 (6.4)	0.52 – 0.67
Difference between t_{lag1} and t_{lag2} (Δt_{lag2}) [hr]	3.32 (9.7)	2.75 – 4.02
Effect of dose on F (power function ^b)	-0.53 (25.4)	-0.79 – -0.27

^aAllometric scaled based weight with power exponent of 0.75 for clearance and 1 for volume of distribution. Estimate is given for a standardized weight of 22 g. ^bF · (dose/dose)⁰

Figure 2. Median DNDI-o690 concentrations on day 1 and 10

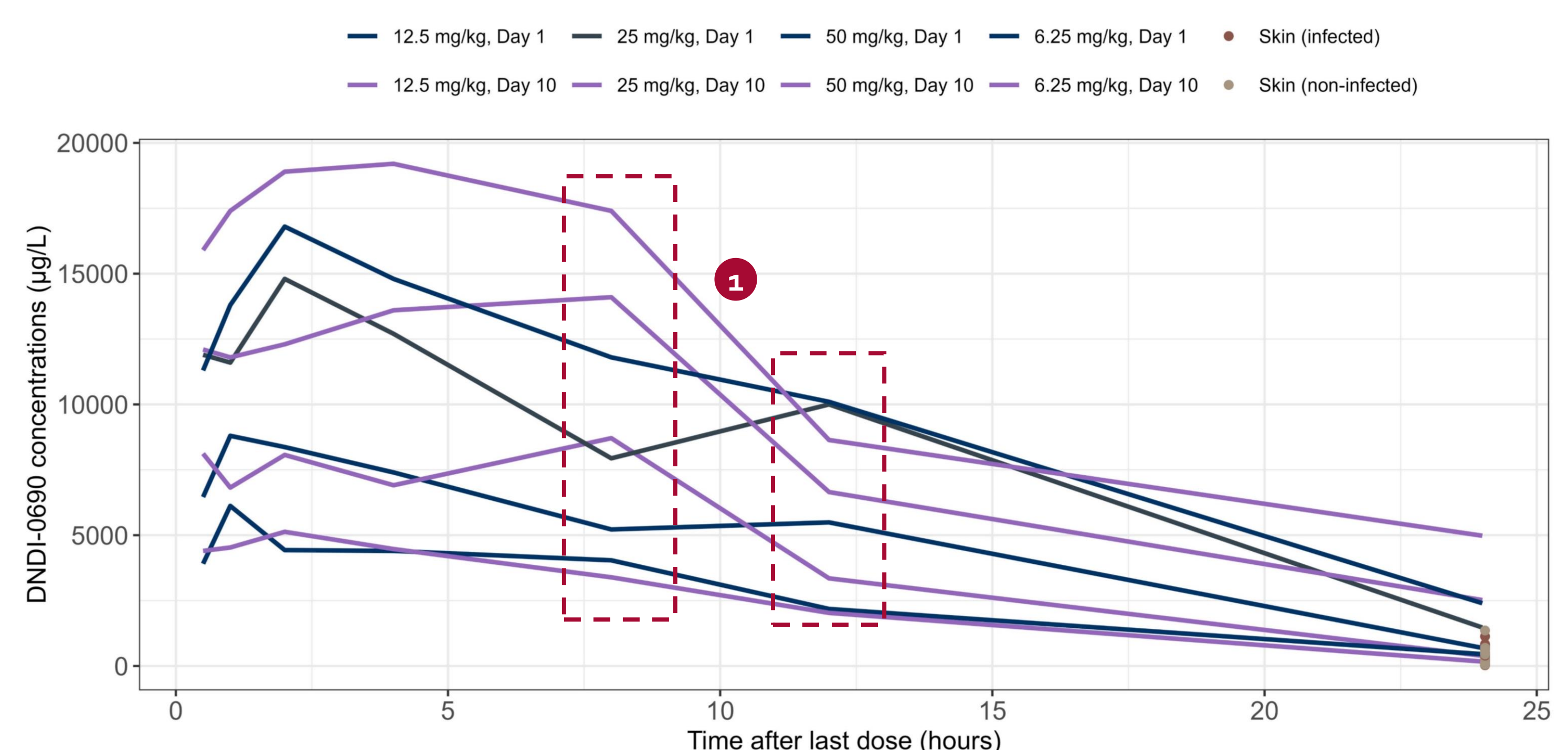
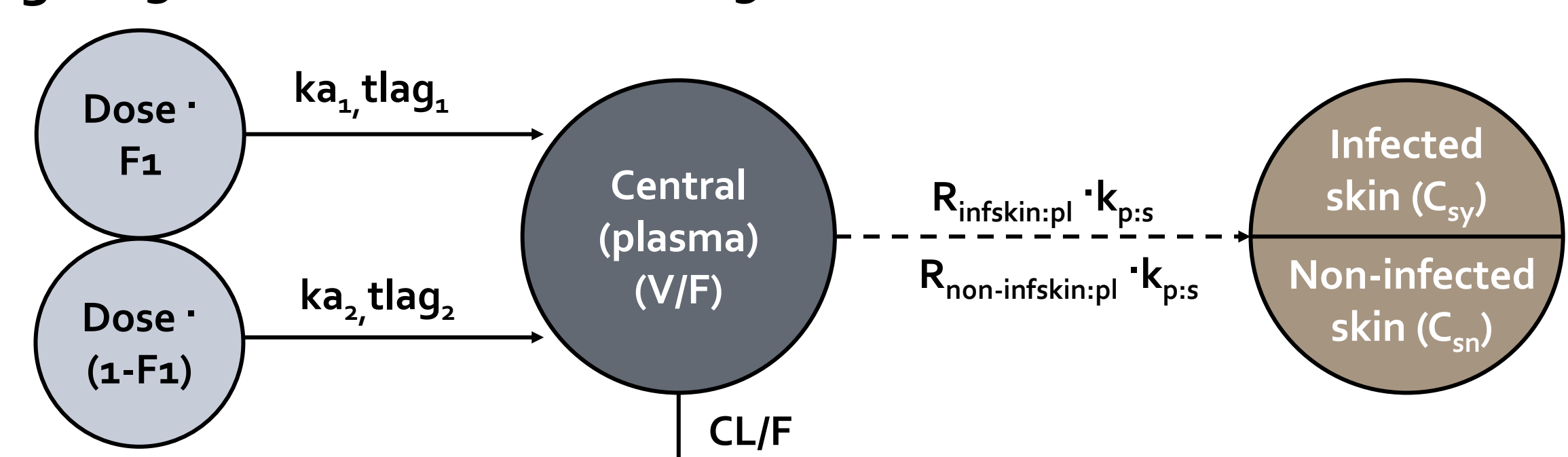


Figure 3. Structure of DNDI-o690 PK model



Conclusions

- DNDI-6148** exhibited non-linear kinetics and penetrated target skin tissue to a lesser degree compared to plasma. However, simulations indicated that exposures were well above the *in vitro* IC50 for the treatment duration at the studied dose levels. The skin to plasma ratio indicated **equal** distribution of DNDI-6148 into infected and non-infected skin.
- Complex absorption PK of **DNDI-o690** was characterized using a sequential double-absorption model. The skin to plasma ratio indicated a slightly higher distribution of DNDI-o690 into **infected** skin when compared to non-infected skin.



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