

Pharmacokinetic-pharmacodynamic analysis of DNDI-6148 in pre-clinical models of visceral leishmaniasis

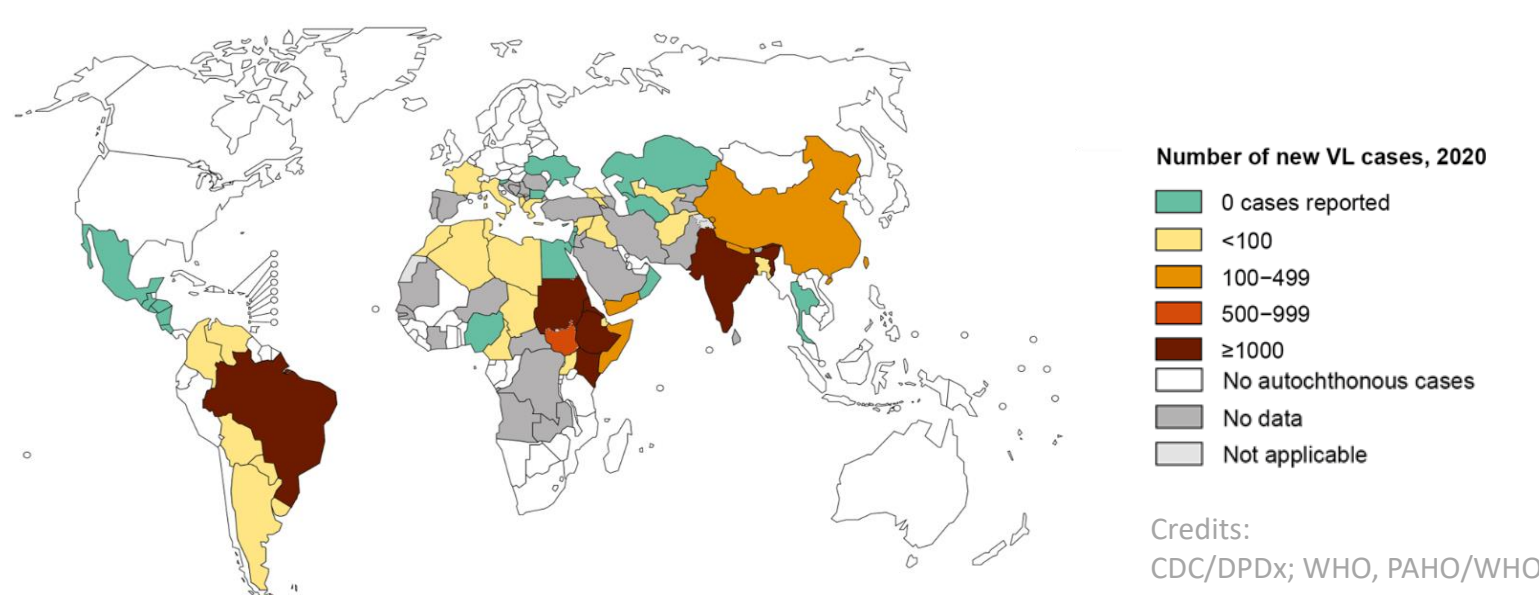
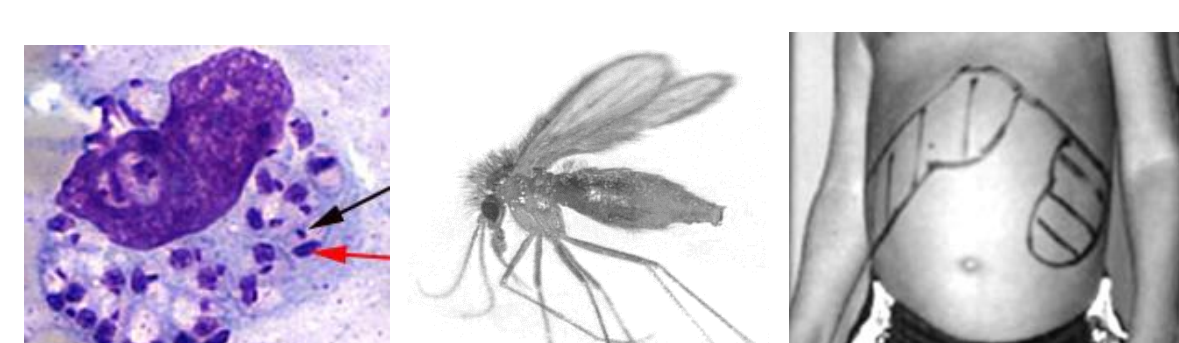
Frauke Assmus^{1,2}, Supada Plitphongphan^{1,2}, Richard M. Hoglund^{1,2}, Charles E. Mowbray³, Stéphanie Brillard³, Eric Chatelain³, Louis Maes⁴, Guy Caljon⁴, Ivan Scandale³, Joel Tarning^{1,2}

Mahidol-Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, ²Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, UK, ³Drugs for Neglected Diseases initiative, Geneva, Switzerland, ⁴Laboratory for Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Belgium

Background

Visceral leishmaniasis (VL, kala azar) is a neglected tropical disease caused by *Leishmania* parasites (*L. donovani* and *L. infantum*) and can be fatal if left untreated [1]. Current therapies have severe limitations, such as cost, toxicity, resistance, and (for some) parental administration. Hence, there is an ongoing, high need for effective new treatment options [2].

20 000 to 40 000 deaths per year



Number of new VL cases, 2020
Credits: CDC/DPdx, WHO, PAHO/WHO

Fig 1. *Leishmania* amastigotes, sand fly, clinical manifestation and geographic distribution of VL [1,3].

The novel benzoxaborole DNDI-6148 is a promising drug candidate for the treatment of VL [4] and has shown anti-leishmanial activity *in vitro* and in pre-clinical *in vivo* models [5]. While DNDI-6148 has entered a Phase 1 clinical trial [6], information on the PK/PD relationship in pre-clinical species is limited.

Objectives

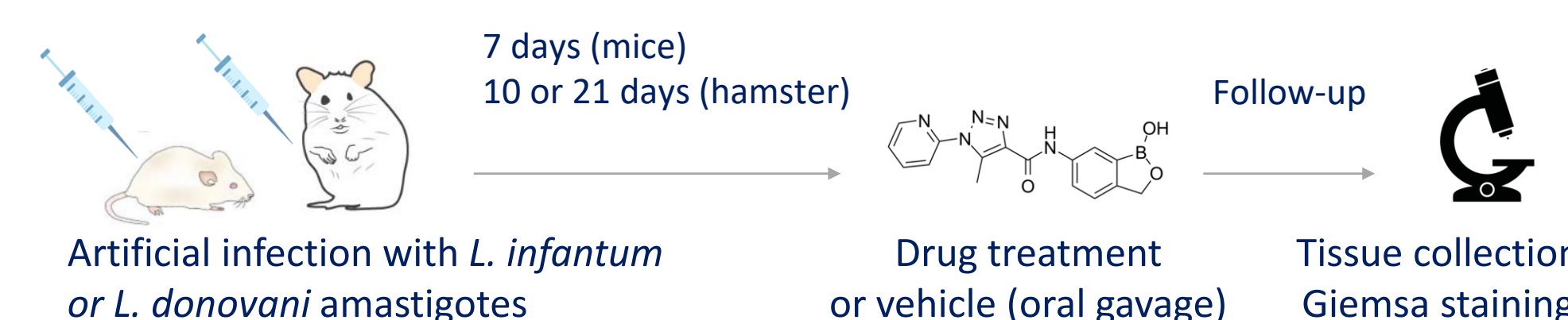
- To characterize the population pharmacokinetic properties of DNDI-6148 in mice and hamster.
- To investigate the relationship between plasma exposure and anti-leishmanial activity in *L. donovani* and *L. infantum*-infected mice and hamster models.

Conclusions

- Exposure-response relationships for DNDI-6148 in *Leishmania*-infected mice and hamsters were successfully quantified.
- Total plasma exposure (AUC_{inf}) was identified as a driver of anti-leishmanial activity.
- Our results provide a valuable tool to aid the dosing selection and design of prospective pre-clinical and clinical trials for VL drug discovery.

Methods

- Satellite PK studies:** Plasma concentration–time data for DNDI-6148 was available from non-infected Balb/c mice (n=38) and Golden Syrian hamsters (n=33).
- Mice:** 6.25, 12.5, 25, 50 mg/kg DNDI-6148 (single dose); **Hamster:** 6.25, 12.5, 25 mg/kg DNDI-6148 arginine salt (single dose); 25, 50mg/kg DNDI-6148 (BID, for 1 or 5 days).
- Population PK models were developed in NONMEM v7.4. and were used to simulate the various dosing scenarios tested in infected mice and hamster.
- Anti-leishmanial activity** (% reduction amastigotes in tissue) was assessed in curative animal models.
- The relationship between simulated drug exposure and anti-leishmanial activity was evaluated by linear and non-linear regression analysis in R v4.0 (screening) and NONMEM (final analysis). Models were compared on the basis of the Akaike and Bayesian information criterion (AIC, BIC), OFV as well as goodness-of-fit diagnostics.



Results & Discussion (PK models)

- DNDI-6148 pharmacokinetics in mice and hamster were well described by two-compartment disposition models with first order absorption.
- Dose \uparrow \rightarrow elimination clearance \downarrow (mice, hamster) and $F \downarrow$ (mice).

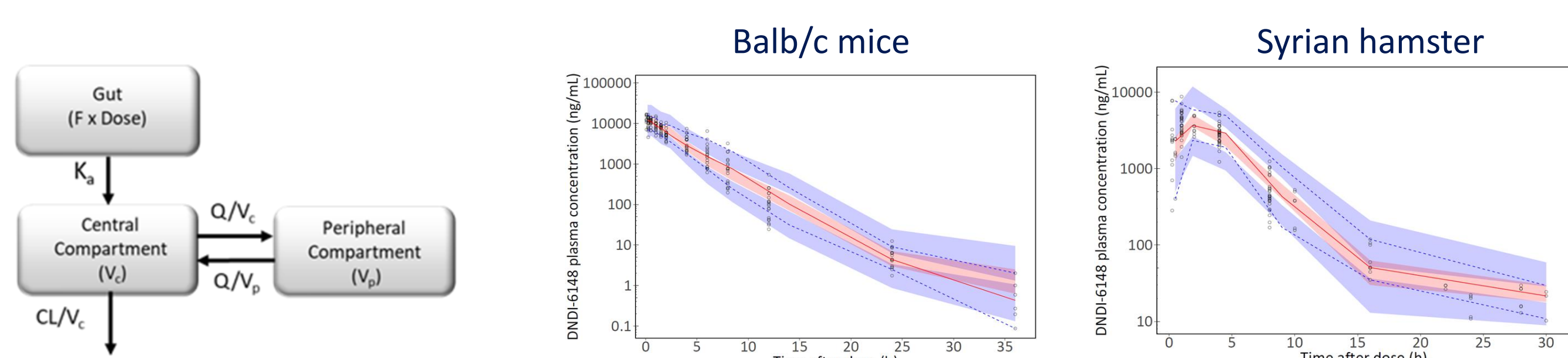


Fig 2. Model structure and visual predictive checks for the final population PK models of DNDI-6148.

Table1. Parameter estimates of the final population PK models of DNDI-6148.

Parameter	Balb/c mice		Syrian hamster	
	Population estimate ^a , (RSE,%) ^b	IIV, %CV ^a (RSE,%) ^b	Population estimate ^a , (RSE,%) ^b	IIV, %CV ^a (RSE,%) ^b
Relative bioavailability, F	1 (fixed)	-	1 (fixed)	16.4 (17.8)
Absorption rate constant, K_A (h^{-1})	8.2 (17.2)	-	0.975 (17.2)	44.4 (25.6)
Elimination clearance, CL/F (mL/h) ^c	6.99 (4.68)	16.2 (9.64)	147 (4.37)	-
Central volume of distribution, V_C/F (mL) ^c	16.8 (4.97)	-	345 (10.9)	-
Inter-compartmental clearance Q/F (mL/h) ^c	0.0359 (19.5)	-	7.45 (12.2)	-
Peripheral volume of distribution, V_P/F (mL) ^c	0.389 (11.8)	-	411 (31.2)	-
Dose effect on CL/F ^d	-0.0184 (11.0)	-	-0.0082 (24.9)	-
Dose effect on F ^d	-0.0108 (19.4)	-	-	-
Residual unexplained variability, σ	0.16 (5.89)	-	0.16 (6.51)	-

^aNONMEM estimate; ^bbased on sampling importance resampling; ^c allometric scaling on clearance & volume parameters; ^dexponential function

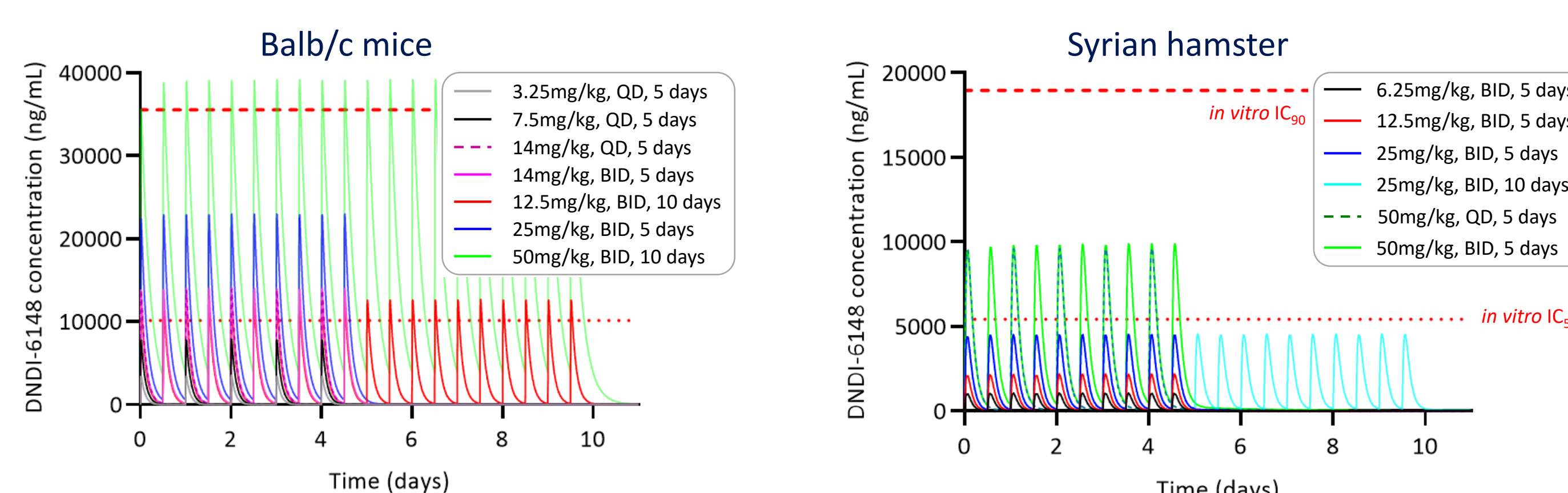


Fig 3. Simulations of DNDI-6148 exposure in plasma for different treatment arms, based on the final PK models of DNDI-6148 in mice (weight 20g) and hamster (weight 100g). *In vitro* IC_{50} and IC_{90} were scaled to account for plasma protein binding in mice ($f_{unbound} = 6.6\%$) and hamster ($f_{unbound} = 12.37\%$).

Results & Discussion (PK/PD models)

- The relationship between plasma exposure and reduction in amastigote burden was best described by an E_{MAX} (mice) and sigmoidal E_{MAX} model (hamster).
- Total plasma exposure (AUC_{inf}) was identified as the better predictor of anti-leishmanial activity as compared to C_{MAX} or time above IC_{50} or IC_{90} .
- L. infantum* showed a higher sensitivity to DNDI-6148 compared to *L. donovani*.

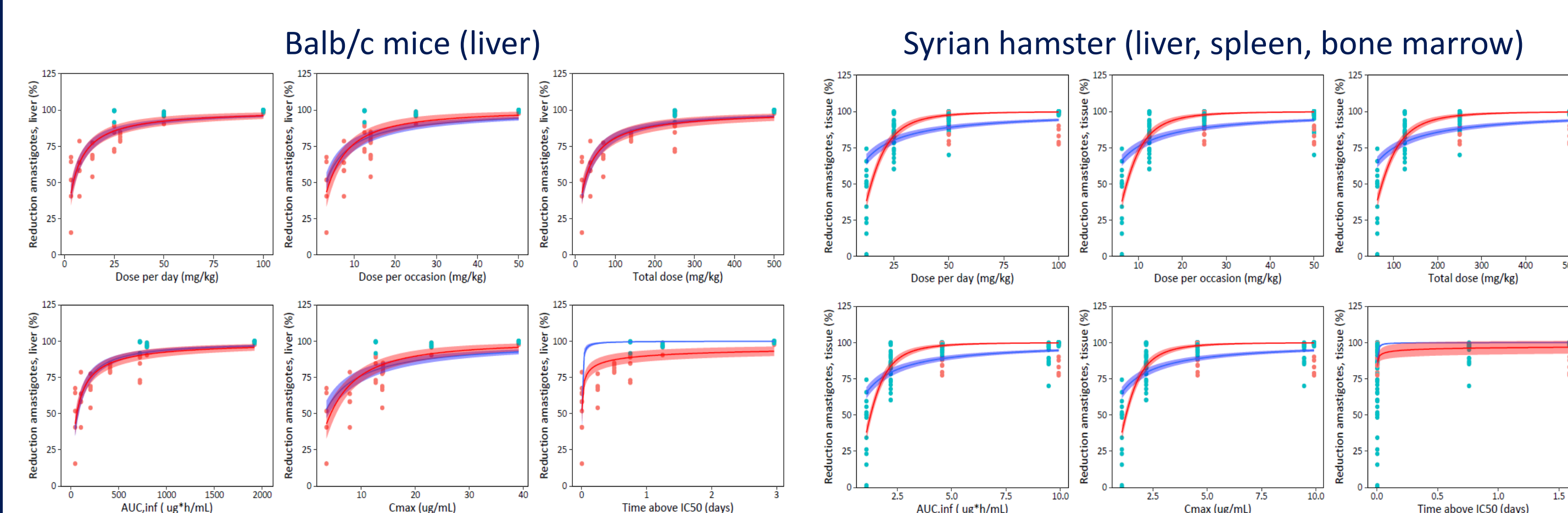


Fig 4. Relationship between different DNDI-6148 exposure variables and parasite reduction in tissue (assumptions: $E_0=0\%$, $E_{MAX}=100\%$).

Table2. Parameter estimates for the E_{MAX} (mice) and sigmoidal E_{MAX} (hamster) models.

Parameter ^a	Balb/c mice	Syrian hamster ^b	
	Liver	Liver & spleen	Bone marrow
Hill slope	1 (fixed)	3.81	1.49
AUC_{50} (<i>donovani</i>) ($\mu g \cdot h/mL$)	66.0 ^c	106	62.7
AUC_{50} (<i>infantum</i>) ($\mu g \cdot h/mL$)		55.4	32.8

^aNONMEM estimates; ^bTissue – specific differences might be due to different parasite quantification methods for liver/spleen (weight considered) and bone marrow; ^cno significant difference in parameters between parasite strains

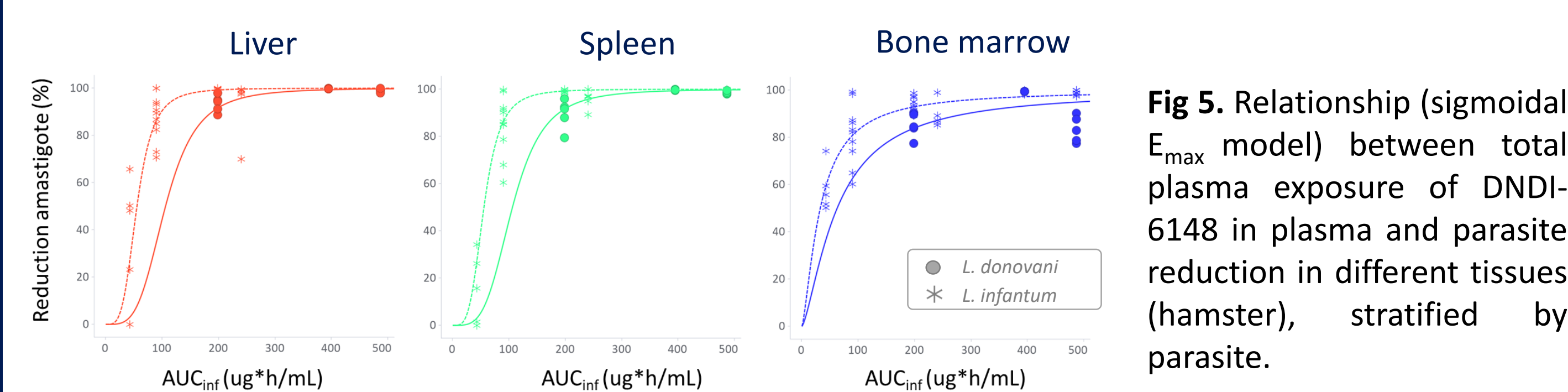


Fig 5. Relationship (sigmoidal E_{max} model) between total plasma exposure of DNDI-6148 in plasma and parasite reduction in different tissues (hamster), stratified by parasite.

References

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