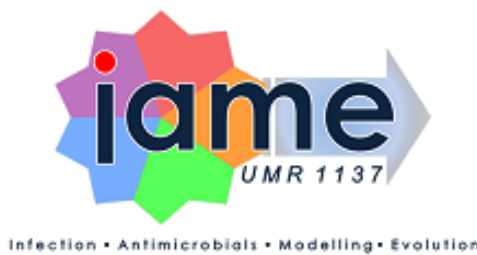


Favipiravir pharmacokinetics in non-human primates: insights for future efficacy studies against hemorrhagic fever viruses

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Funded by the Horizon 2020 framework programme of the European Union

Introduction

- Favipiravir (FPV) is a nucleotide analogue with a strong antiviral efficacy in vitro and in small animal models against several viruses responsible for haemorrhagic fever (HF), including Ebola virus.
- FPV is known to inhibit the enzyme responsible of its own metabolism, aldehyde oxidase.
- The aim of this work was to characterize the complex PK of FPV in non-human primates (NHP) in order to guide future efficacy studies in large animal model.

Methods

Data:

Four studies in cynomolgus uninfected macaques with multiple sources of variability: breeds, gender, loading doses (200 – 300 mg/ kg BID), maintenance doses (60 – 180 mg/kg BID), study duration, sampling times (Fig 1).

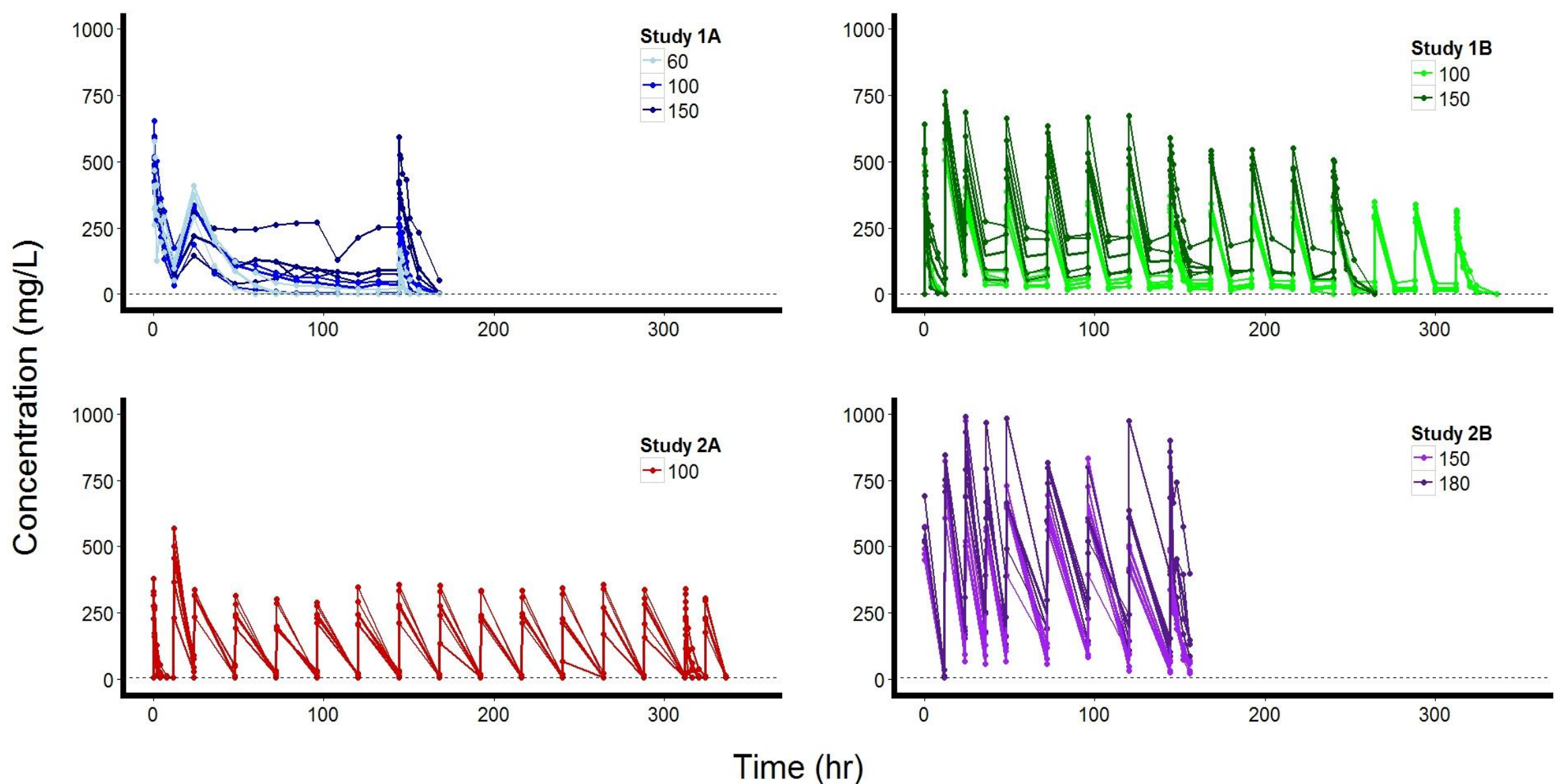


Figure 1: Strategy used to build the pharmacokinetic model

Pharmacokinetic model building:

A PK model was developed to incorporate the sources of variabilities. Structural model building strategy, error model, random effects and covariates selection were based on the Bayesian Information Criterion (Fig 2). Parameter estimation was done using non-linear mixed effect models with Monolix software (4).

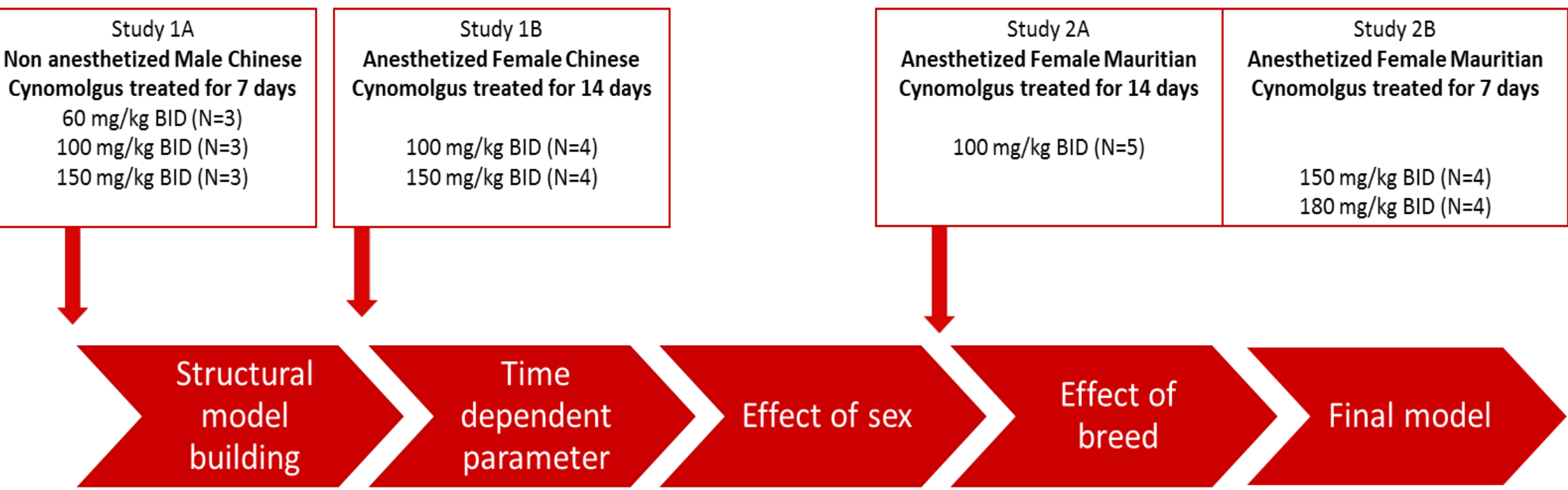


Figure 2: Strategy used to build the pharmacokinetic model

Dosing regimen against various HF viruses:

- Using the final PK model and the mlxR package (5), simulation of various dosing regimens were performed including dose increase after day 7 to maintain constant exposure until day 14
- Accounting for a binding fraction of 50%, FPV's predicted free trough concentrations were compared to EC₅₀ of HF viruses: Ebola virus, Lassa virus, Marburg virus, Rift valley fever virus, Junin virus and Crimea-Congo haemorrhagic fever virus.

References

1. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral Res. 2013;100:446–54. 2. Oestereich L, Lüdtkke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. 2014. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral research 105:17–21. 3. Gowen BB, Wong M-H, Jung K-H, Sanders AB, Mendenhall M, Bailey KW, et al. In vitro and in vivo activities of T-705 against arenavirus and bunyavirus infections. Antimicrob. Agents Chemother. 2007;51:3168–76. 4. Lavielle M. 2014. Mixed effects models for the population approach: models, tasks, methods and tools. CRC Press. 5. Lavielle M, Kuate R, Francois R, Bellal F. mlxR: Simulation of Longitudinal Data 2015 [cited 2015 Dec 22]. Available from: <https://cran.r-project.org/web/packages/mlxR/index.html>

Results

Pharmacokinetic model:

A model including enzyme mediated elimination with concentration dependent inhibition was selected. The decrease in FPV concentration over time was captured using assuming a time dependent variation in enzyme kinetic.

Table: Pharmacokinetic model parameter estimates.

Fixed effect	Estimation (% rse)	Standard deviation of Random effect (% rse)
V _d (L/kg)	0.359 (2.8)	0.138 (14.5)
k (h ⁻¹)	0.0654 (6.6)	0.231 (15.2)
V _{max} Mauritian breed (h ⁻¹)	2.85 (9.8)	0.239 (13.0)
V _{max} Chinese breed (h ⁻¹)	1.25 (8.8)	
k _{el} Mauritian breed (mg ⁻¹ .L)	0.179 (10.1)	–
k _{el} Chinese breed (mg ⁻¹ .L)	0.100 (9.5)	
k _{out} Male (h ⁻¹)	0.036 (6.4)	–
k _{out} Female (h ⁻¹)	0.0235 (6.0)	
λ (h ⁻¹)	0.00155 (18.7)	0.857 (16.3)
Residual error	Estimation (rse)	
additive (mg/L)	2.77 (7.9)	
proportional	0.155 (3.1)	

Covariate effect:

Mauritian macaques had a higher enzyme dependent elimination constant Vmax (2.85 h⁻¹) than Chinese macaques (1.25 h⁻¹), explaining the exposure discrepancy observed between the two breeds. Another breed effect was found on k_{el} and gender effect on k_{out}.

Simulation of FPV dosing regimens in regard of drug EC50s:

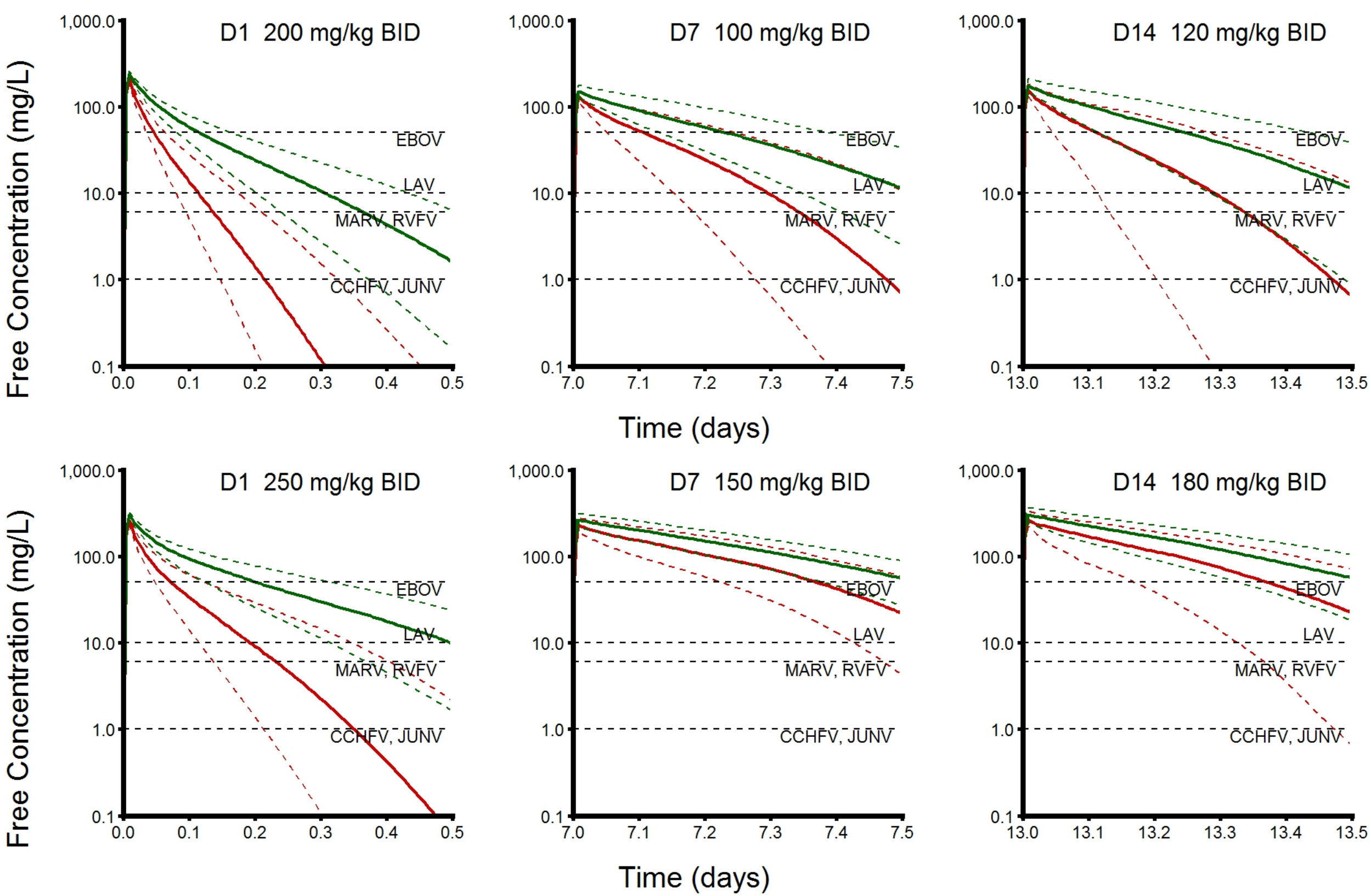


Figure 3: Prediction of FPV plasma free concentration of favipiravir in female Chinese (green) and Mauritian (red) cynomolgus with various dosing regimen, related to HF viruses EC₅₀s.

- Favipiravir PK is largely nonlinear over doses and time, leading to a 20-50% decrease in concentrations after day 7, and is also affected by macaque breed.
- Maintenance dose of **100 and 130 mg/kg BID** in Chinese and Mauritian macaques, respectively, are predicted to achieve median trough concentrations above EC₅₀ of most targeted viruses (including Marburg and Lassa virus) until day 7, whereas larger doses of **150 and 180 mg/kg BID**, respectively, may be required for Ebola virus.
- About 20% increase in dose after day 7 may be required to maintain trough concentration up to day 14.

Conclusion

Our results shows that favipiravir PK could be captured by a mechanistic enzyme based model. In absence of intracellular data, dose recommendation was based on protein unbound plasma concentrations, but the relevance of this approach will need further efficacy studies.