

Parasitemia clearance modeling following Ferroquine administration in *P. falciparum* infected patients

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Status and Problem

- Ferroquine (FQ):** an anti-malarial drug currently under development in combination with OZ439 by Sanofi and Medicines for Malaria Venture (MMV) as a single dose treatment for uncomplicated malaria
- Objective of this analysis:** to develop and qualify a population pharmacokinetic-pharmacodynamic (PKPD) model for FQ and its active metabolite SSR97213 to describe early parasitemia clearance using data from a Phase II study in *P. falciparum* infected patients (DRI10382). A population pharmacokinetic (PopPK) model of both FQ and its active metabolite SSR97213 after oral administration was already developed internally from a pool of phase I & II studies that included healthy adult subjects, and malaria patients (both adult and children).

Pharmacometric Approach

- Data:** coming from DRI10382 – FQ alone arm – Phase IIb study
 - 79 symptomatic patients (*from 4 to 74 years old*)
 - One dosing regimen: *4mg/Kg (or 200 mg from 50 kg) one a day x 3 days*
 - FQ and metabolite blood concentration measurements
 - Microscopy parasitemia measurement (*up to day 63 – 17/patients – 1329 in the analysis database, including 48% of data below Limit of Quantification (LOQ)*)
 - 39% of patients received rescue therapy during the study
 - 44% of patients were re-infected (new infection) during the study
 - 1 recrudescence of initial infection, and 2 re-emergences of unknown origin (Polymerase Chain Reaction (PCR) failure)
- Analysis methodology:**
 - Non Linear Mixed Effects model – Monolix 4.3.3
 - Joint sequential approach: population parameters of PopPK model set to values estimated in PopPK analysis
 - Parasite counts after rescue therapy or re-infection excluded

Results and Discussion

1- Final PKPD model

- PK of FQ and its active metabolite described respectively by a 3-and-2-compartment model
- PD endpoint: N= parasite counts restricted to the initial genotype that first infected the patient (par/μL)
- N_{t=0} set to the first parasite count (at screening): used as regressor
- Periodic oscillation (OSCI) during growth and degradation phase, and a recurrence threshold (REC)
- Drug effect linked to Ferroquine concentrations C_{FQ} (adding active metabolite effect did not improve the fit)
- Time-to-event (TTE) model describing rescue medication intake linked to first parasitemia infection:
 - censoring of rescue therapy times in case of reinfection
 - hazard function *h(t)* depending on time and parasitemia

$$\frac{dN}{dt} = N \cdot (Kg - K_{kill}) \times OSCI \times REC$$

$$K_{kill} = K_{kill,FQ} \cdot \frac{C_{FQ}}{EC_{50,FQ} + C_{FQ}}$$

$$OSCI = 1 + AMP \cdot \cos\left(2\pi \cdot \left(\frac{t-T_0}{48 \text{ hr}}\right)\right) \text{ with } T_0 = 48 \cdot \frac{e^\varphi}{1+e^\varphi}$$

$$REC = \mathbb{1}_{(N > Thr)}$$

$$h(t) = \gamma_0 + \gamma \cdot \log_{10}(N(t)) \cdot \mathbb{1}_{t \geq Tlag}$$

Table 1: Final parameter estimates

	Parameter (RSE)	IIIV (RSE)
<i>Kg</i> (h ⁻¹)	0.06	
<i>K_{kill,FQ}</i> (h ⁻¹)	0.200 (6)	0.417 (11)
<i>EC_{50,FQ}</i> (ng/ml)	6.69 (31)	1.34 (17)
<i>φ</i>	-0.05	0.956 (6)
<i>AMP</i>	1.45 (13)	1.18 (7)
<i>Thr</i> (Parasites/μL)	2.10 ⁻⁷ (fix)	
<i>γ₀</i>	0.000001 (fix)	
<i>γ</i>	0.00151 (21)	0.503 (31)
<i>Tlag</i> (h)	31.6 (24)	-
<i>σ</i>	0.581 (2)	

Kg: growth rate; *K_{kill,FQ}*: maximal kill rate due to FQ; *EC_{50,FQ}*: FQ concentration to reach 50% of *K_{kill,FQ}*; *φ*: parameter describing phase T₀ of oscillations of amplitude *AMP*; *Thr*: parasite threshold; *γ₀*, *γ* & *Tlag*: intercept, parasite effect & lag time in hazard function for rescue medication model; *σ*: Additive Residual Error on log₁₀(N)

2- Model qualification

- Parameters estimation: plausible values & good estimation (RSE < 31%) (Tab.1)
- VPC for this PK-PD-TTE model: model correctly predicts parasitemia for early times (Fig.1)
- Rescue medication: rather good prediction despite high censoring rate (Fig.2)

Fig.1: VPC of the final PK-PD-TTE model

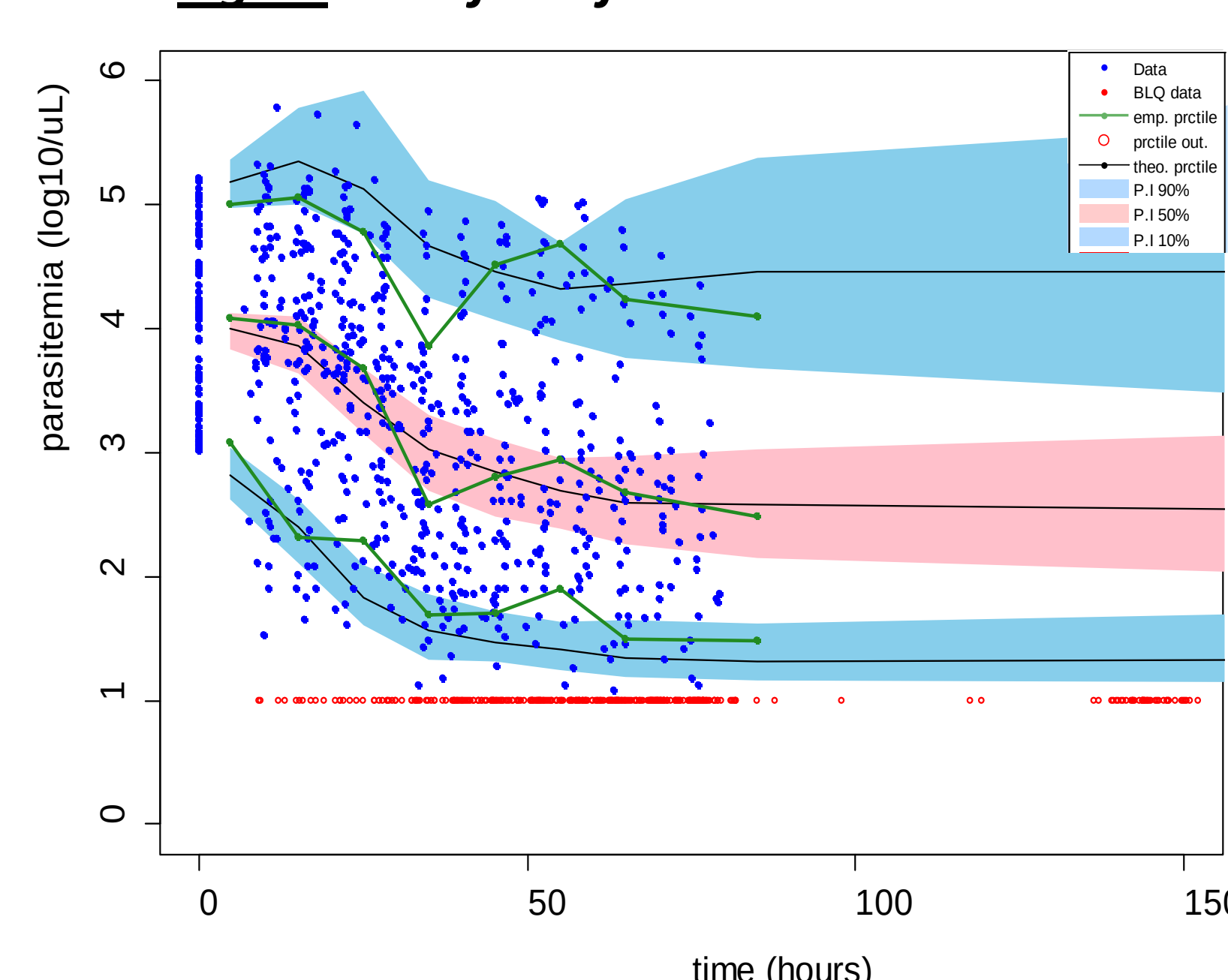
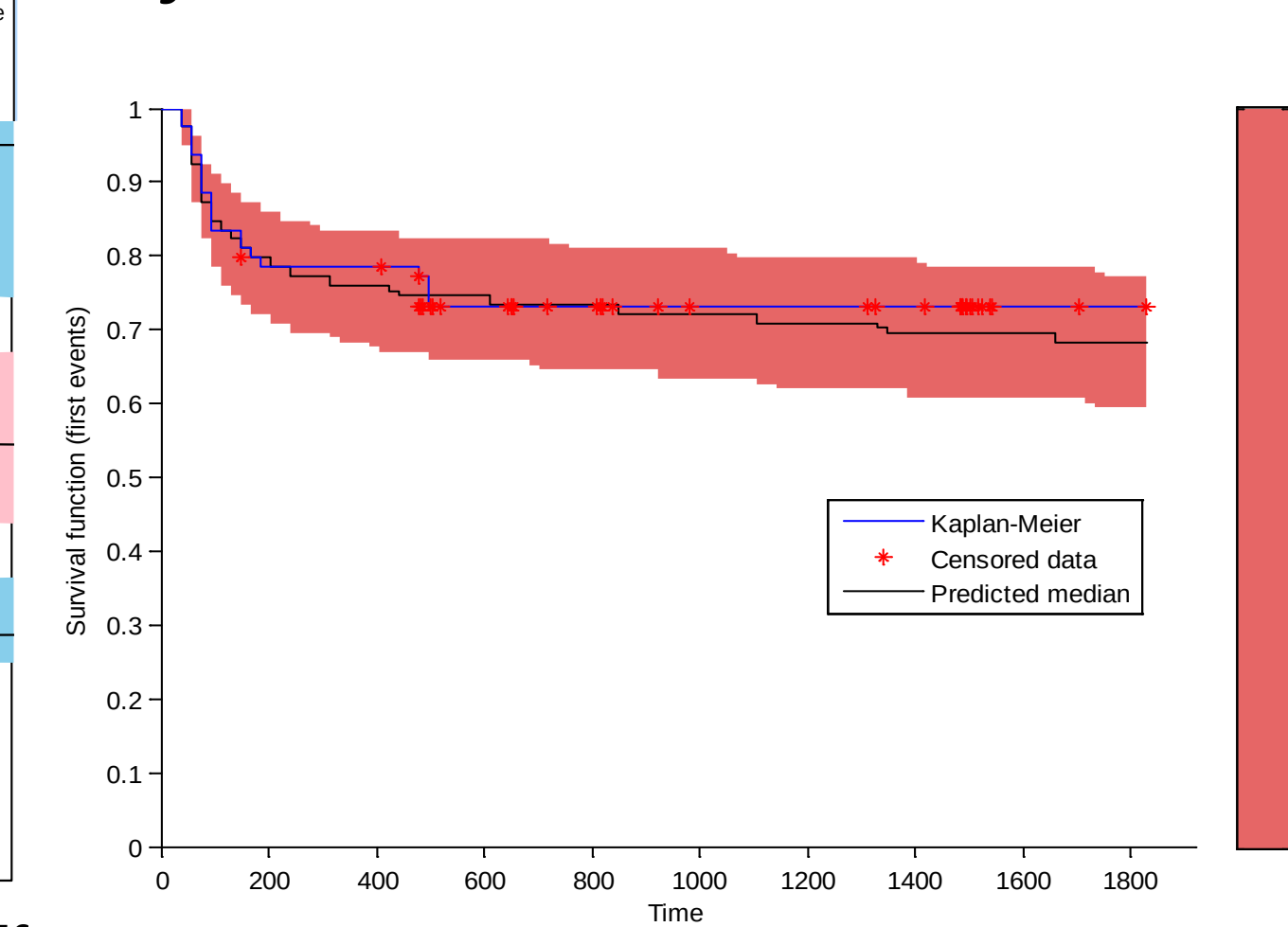


Fig.2: Kaplan-Meier plot of the intake of rescue medication linked to first infection



3 - Simulations based on this model

- Simulated Parasite Reduction Ratio after 48h (*PRR48*) and Cure rate at Day28 are in agreement with the observed values (Fig. 3 and 4)
 - *PRR48* = $-\log_{10}(N_{48}/N_0)$ (patients rescued -observed (5) or simulated- before 48h excluded)
 - *Cure rate*_{d28} = $\frac{\text{nb of patients with } N_{d28} < LOQ \text{ \& without rescue therapy}}{\text{total number of patients}}$ (patients rescued -observed or simulated- before day28 considered as failure; patients reinfected before day28 excluded from Cure rate calculation)
- Median of simulated *PRR48* (rescue therapy excluded) in African adults increases with FQ single dose of 400mg, 600mg and 900mg: *PRR48*_{SD400}=2.4, *PRR48*_{SD600}=2.6, *PRR48*_{SD900}=2.7, and is higher as compared to 200mg x 3 days (2.1).

Fig.3: comparison of simulated (boxplot) and observed (blue point) PRR48

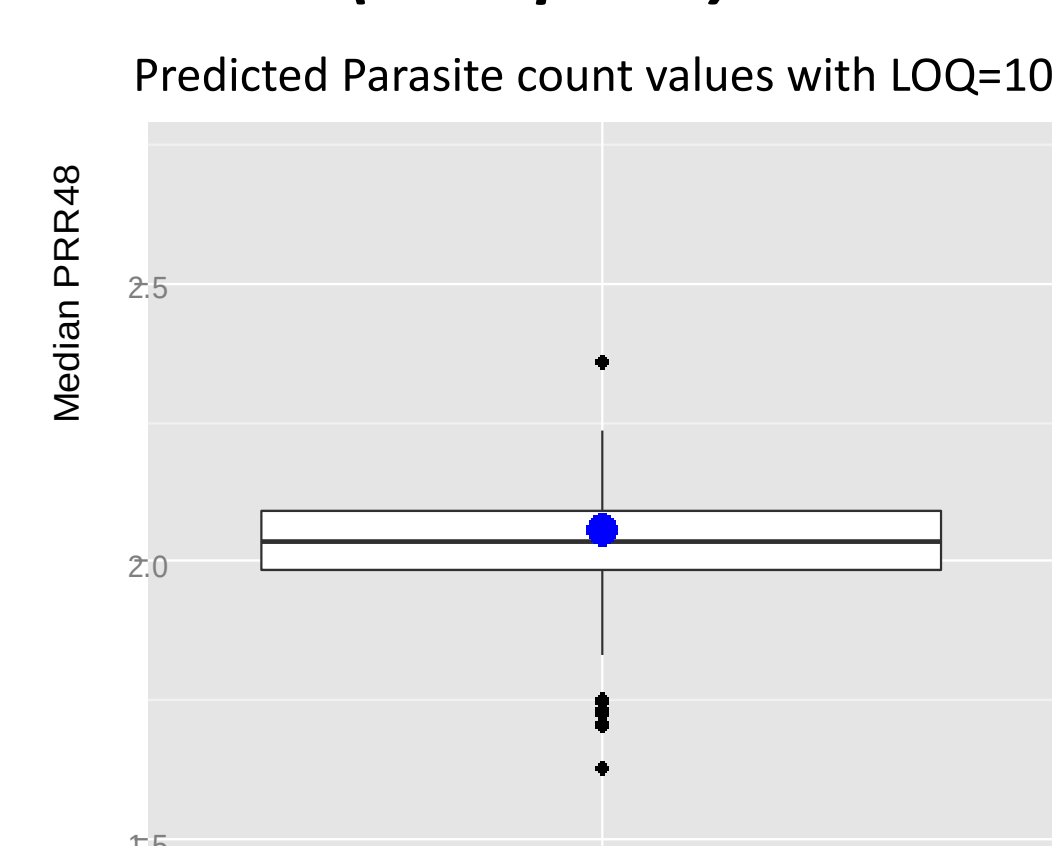
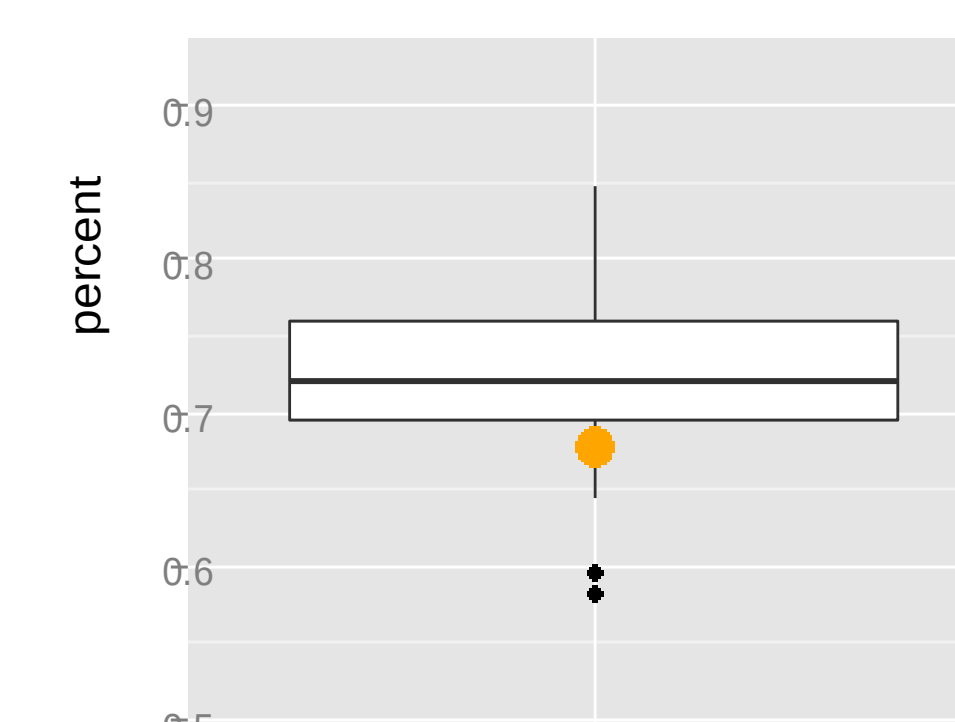


Fig.4: comparison of simulated (boxplot) and observed (orange point) cure rate at Day 28 linked to first infection



Conclusions and Critical Impact

Based on FQ alone data from a phase IIb study, we have developed a PKPD-TTE model linking FQ blood concentration to parasitemia clearance and intake of rescue medication. *PRR48* is predicted quite well but cure rate at Day 28 is slightly over-predicted. Given the paucity of recrudescence and the limited PD data at time of recrudescence, there is some uncertainty in *EC50*. This model will be improved including single dose data from new studies and is a first step for developing a PKPD model for FQ-OZ439 combination.

Acknowledgments

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