



QIMR Berghofer
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Translational tools for Early Development of Antimalarials: The Human Malaria Challenge Model

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Outline

- The context of antimalarial drug development
 - The Target Product Profile
 - The existential threat of artemisinin resistance
 - Impediments to efficacy testing candidate antimalarials in humans
- How do the human challenge models help development of new antimalarial drugs (& vaccines)
 - Study endpoints
 - Collection of key data for pharmacometric analysis
- Future prospects

The target product profile

Burrows *et al. Malar J* (2017) 16:26
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Malaria Journal

REVIEW

Open Access



New developments in anti-malarial target candidate and product profiles

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Abstract

A decade of discovery and development of new anti-malarial medicines has led to a renewed focus on malaria elimination and eradication. Changes in the way new anti-malarial drugs are discovered and developed have led to a dramatic increase in the number and diversity of new molecules presently in pre-clinical and early clinical development. The twin challenges faced can be summarized by multi-drug resistant malaria from the Greater Mekong Sub-region, and the need to provide simplified medicines. This review lists changes in anti-malarial target candidate and target product profiles over the last 4 years. As well as new medicines to treat disease and prevent transmission, there has been increased focus on the longer term goal of finding new medicines for chemoprotection, potentially with long-acting molecules, or parenteral formulations. Other gaps in the malaria armamentarium, such as drugs to treat severe malaria and endectocides (that kill mosquitoes which feed on people who have taken the drug), are defined here. Ultimately the elimination of malaria requires medicines that are safe and well-tolerated to be used in vulnerable populations: in pregnancy, especially the first trimester, and in those suffering from malnutrition or co-infection with other pathogens. These updates reflect the maturing of an understanding of the key challenges in producing the next generation of medicines to control, eliminate and ultimately eradicate malaria.

Keywords: Malaria, *Plasmodium*, Elimination drug discovery, Eradication drug discovery, Medicines, Target candidate profile, Target product profile

Burrows *et al. Malaria J.* 2017

TCP1 Case management of uncomplicated malaria



TCP1 Case management of severe malaria



TCP3 Case management of relapsing malaria



TCP4 Chemoprotection



TCP5 gametocides

TCP6 endectocides



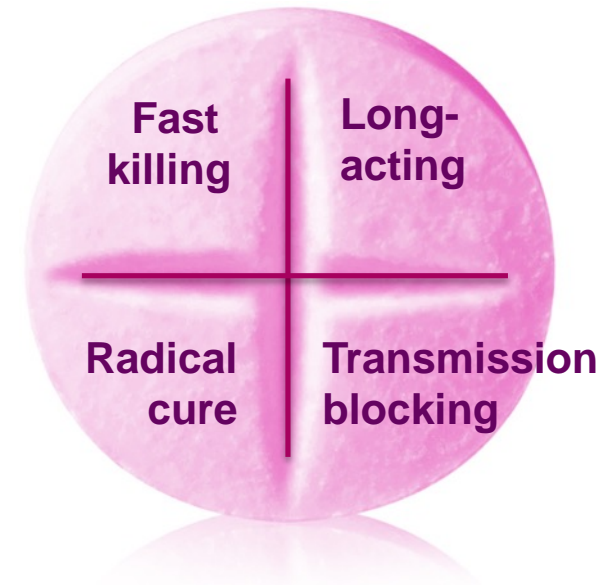
Chemoprevention of vulnerable populations



Complex considerations in the development of new antimalarials

- Only co-formulations will be developed
 - Matched or mismatched PK profiles?
 - Drug activity
 - Fast + slow killer?
 - Synergy/Antagonism
 - Selection of resistance
 - Interacting toxicology issues
- Pediatric and pregnant target population

SERCaP



Spread of multidrug resistant malaria parasites in the Greater Mekong Subregion

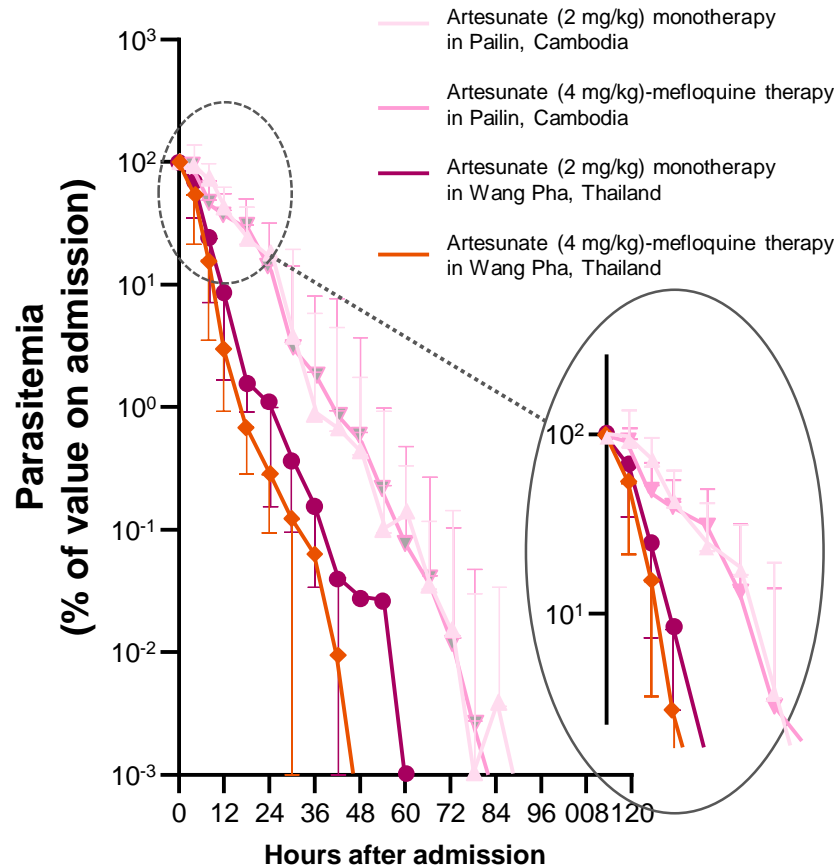
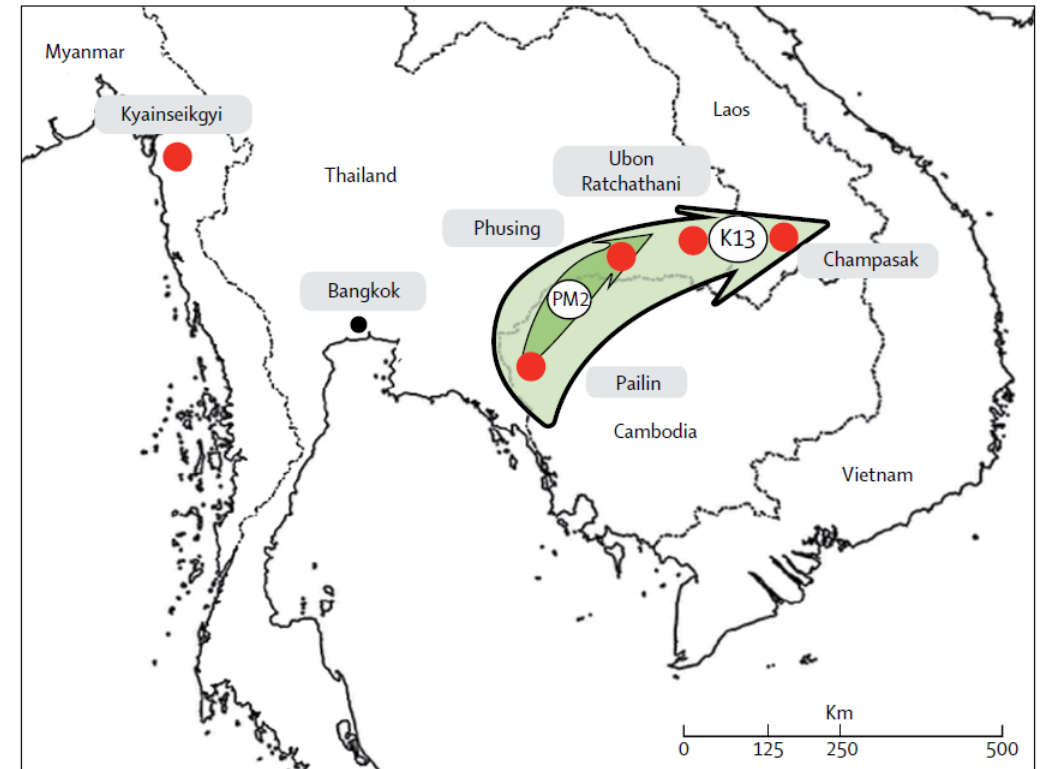


Figure 4 Normalized *P. falciparum* parasite clearance curves showing the fraction of initial parasitemia versus time in patients treated with artesunate in Western Cambodia and Western Thailand. Parasite clearance was significantly slower in Western Cambodia.

Dondorp et al. (2009) NEJM 361: 456-67



Spread of parasites resistant to both components of Artemisinin Combination Therapy

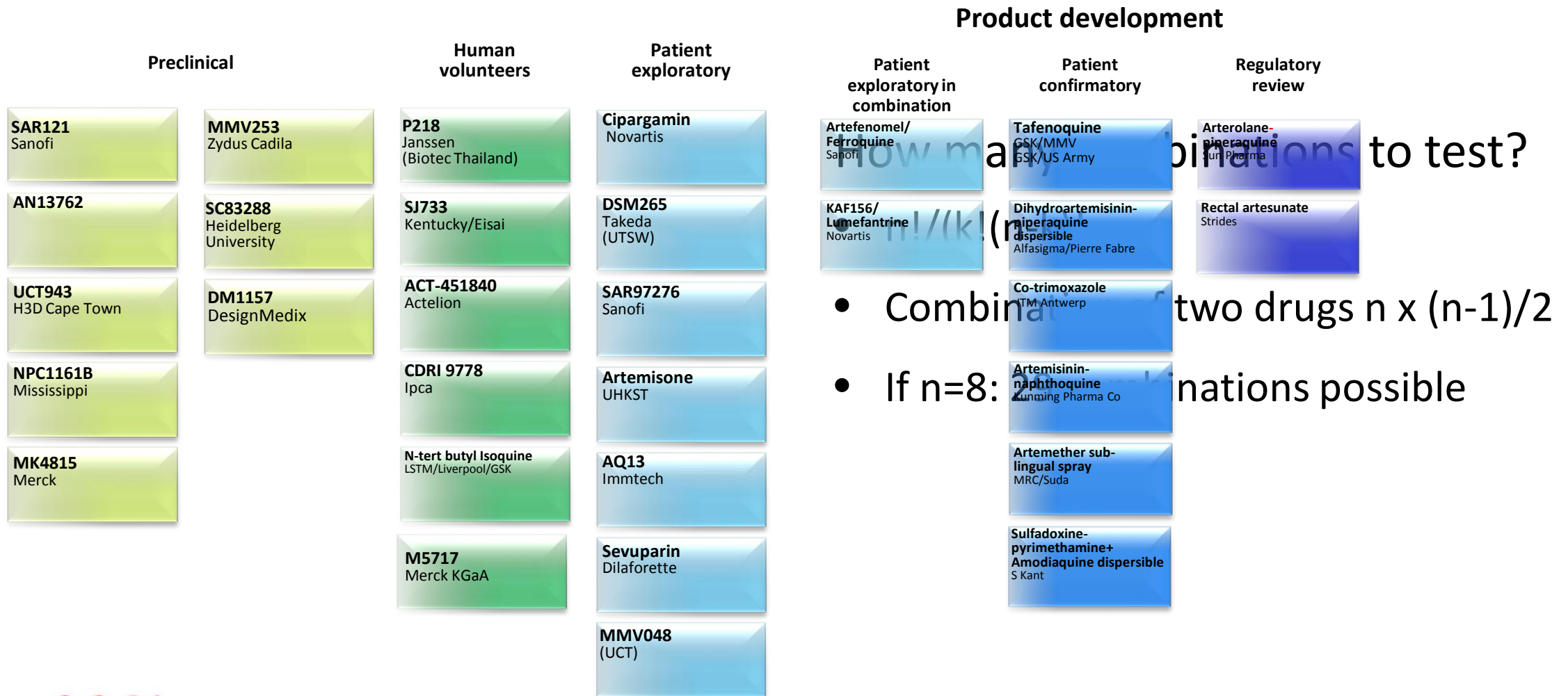
Imwong, M., et al., (2017) Lancet Infectious Diseases 17: 491-497
 Amaratunga C, et al., (2016) Lancet Infect Dis. 16:357-65

Difficulties in executing efficacy studies of new antimalarials: Remoteness of potential Phase II trial sites



“We often have to contend with difficult terrain, muddy roads, harsh weather, difficulty communicating with local villagers who have little knowledge of malaria and scarcity of food. The risk of being kidnapped by local bandits is another challenge that we have to face when travelling on a long mobile-team mission to remote villages,” explains Dr Han Min Htet Aung from MAM's malaria project of Yebyu Township.

Finding the right combination from the Global Portfolio of Antimalarials under development



SCIDHu Mouse malaria model

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2009, p. 4533–4536
 0066-4804/09/\$08.00+0 doi:10.1128/AAC.00519-09
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Improved Murine Model of Malaria Using *Plasmodium falciparum* Competent Strains and Non-Myelodepleted NOD-*scid* *IL2R* γ^{null} Mice Engrafted with Human Erythrocytes[▽]

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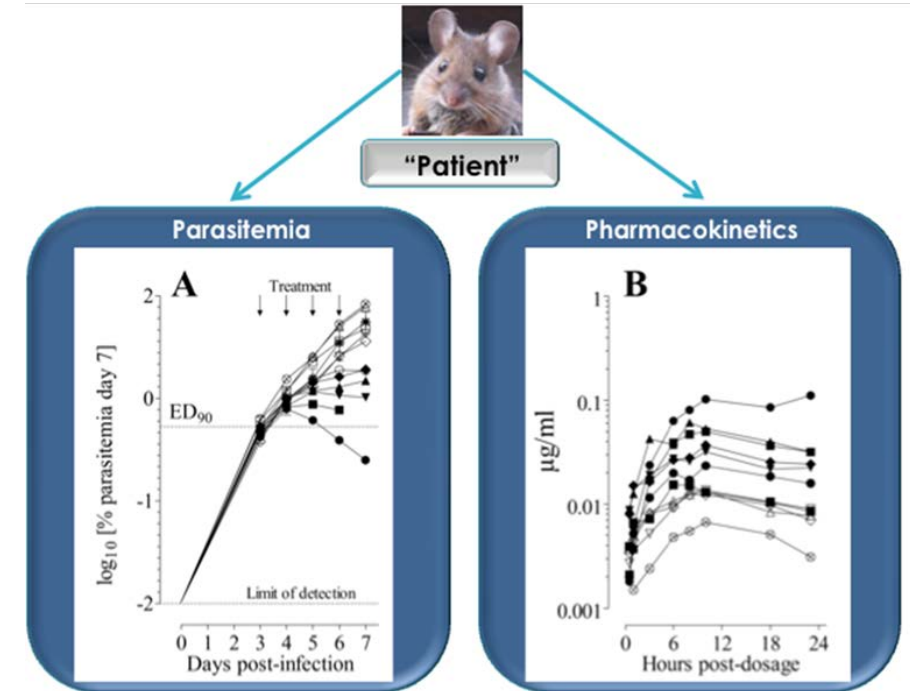
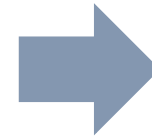
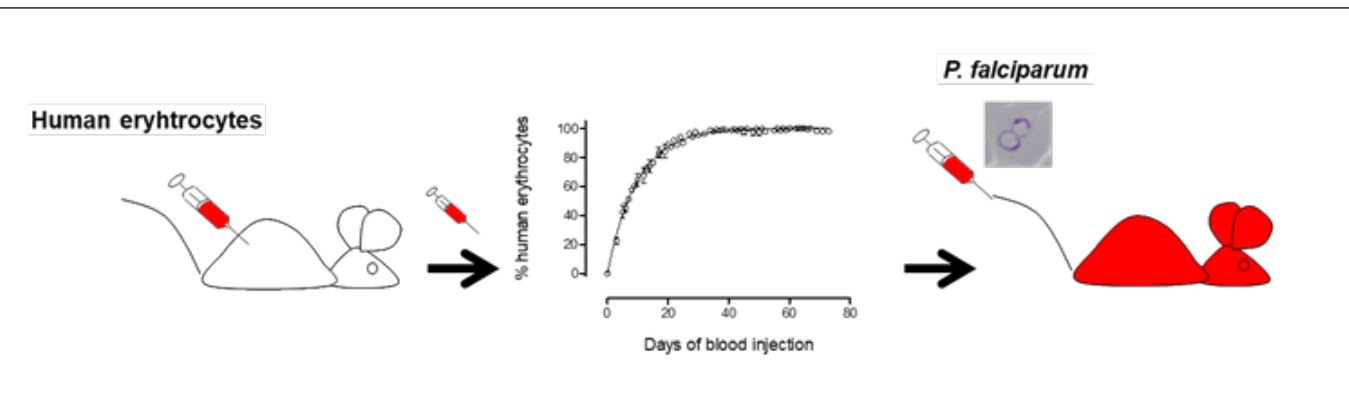
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Murine models of *Plasmodium falciparum* malaria may become crucial tools in drug discovery. Here we show that non-myelodepleted NOD-*scid* *IL2R* γ^{null} mice engrafted with human erythrocytes support an infectious burden up to tenfold higher than that supported by engrafted NOD-*scid* β 2microglobulin γ^{null} mice. The new model was validated for drug discovery and was used to assess the therapeutic efficacy of 4-pyridones, selective inhibitors of *P. falciparum* cytochrome *bc*₁.

PK/PD LINKING THE AMOUNT OF DRUGS IN BLOOD WITH CURE OF MICE

(RECRUDESCENCE ASSESSMENT UP TO DAY 60)



Iñigo Angulo-Barturen





Parasite Inoculation

Test drug

Clinical trial design

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	28
Outpatient		x	x	x	x	x	x	x			+	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Confinement									Q-Pharm																			
Drug Rx																	Rescue Drug Treatment as needed											
PCR (parasites)					x	x	x	x	XXXXXXXXXXXXXXXXXXXX				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PCR (gametocytes)														x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mosquito transmission															x		x		x	x		x	x		x		x	x

Clearance of parasitemia over 48-96 hrs

n=347 subjects

Use of malaria challenge for testing of vaccine efficacy



Vaccine 18 (2000) 1925–1931

Vaccine

www.elsevier.com/locate/vaccine

Effect of vaccination with 3 recombinant asexual-stage malaria antigens on initial growth rates of *Plasmodium falciparum* in non-immune volunteers

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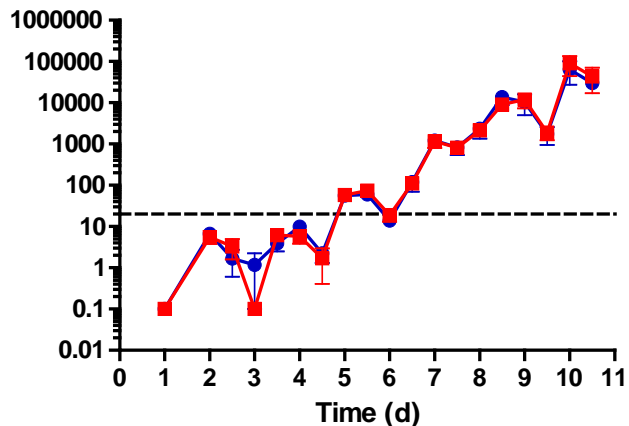
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Payne *et al* JID 2016



OPEN ACCESS Freely available online



Impact on Malaria Parasite Multiplication Rates in Infected Volunteers of the Protein-in-Adjuvant Vaccine AMA1-C1/Alhydrogel+CPG 7909

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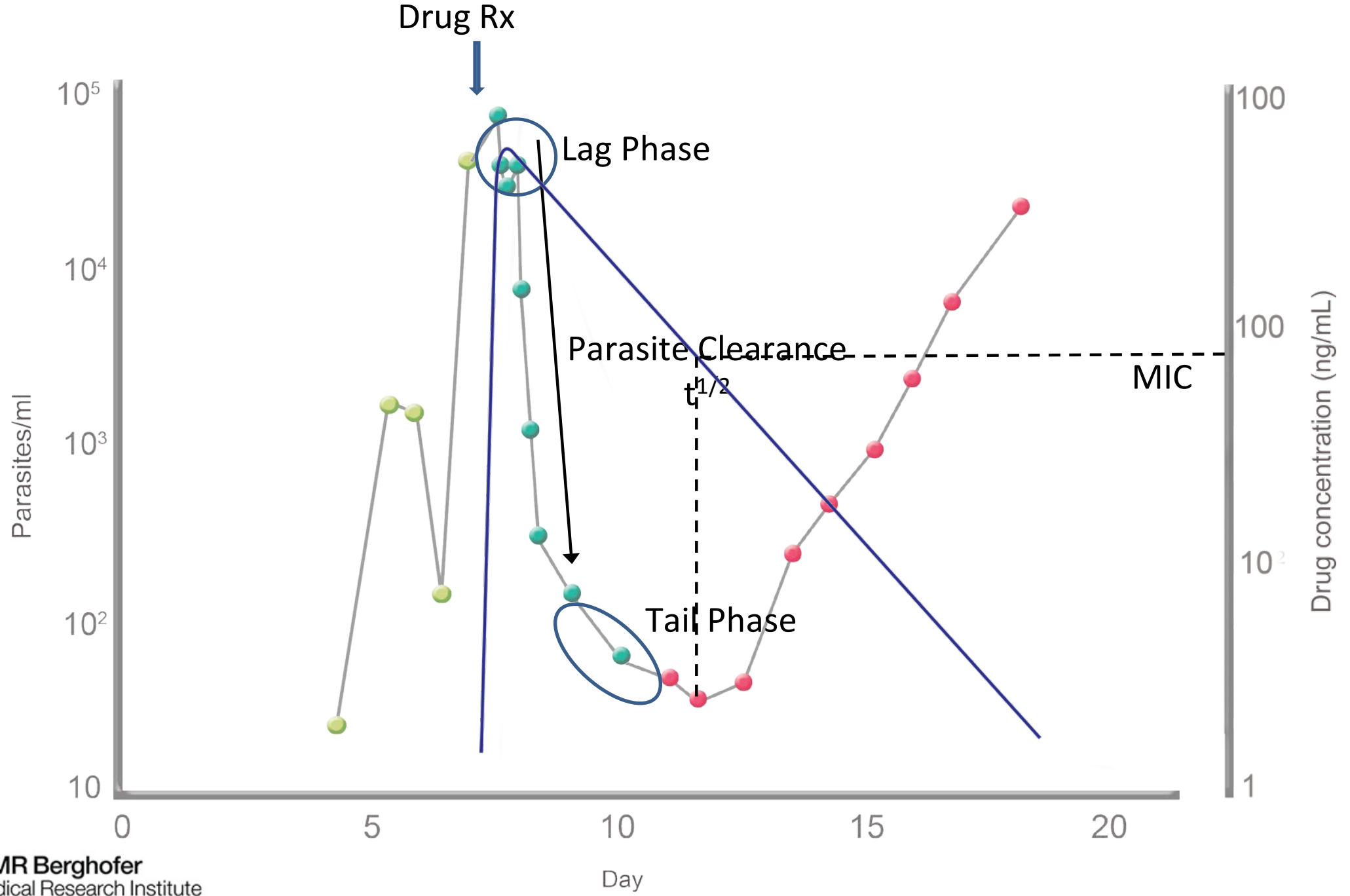
Abstract

Background: Inhibition of parasite growth is a major objective of blood-stage malaria vaccines. The *in vitro* assay of parasite growth inhibitory activity (GIA) is widely used as a surrogate marker for malaria vaccine efficacy in the down-selection of candidate blood-stage vaccines. Here we report the first study to examine the relationship between *in vivo Plasmodium falciparum* growth rates and *in vitro* GIA in humans experimentally infected with blood-stage malaria.

Methods: In this phase I/IIa open-label clinical trial five healthy malaria-naïve volunteers were immunised with AMA1/C1-Alhydrogel+CPG 7909, and together with three unvaccinated controls were challenged by intravenous inoculation of *P. falciparum* infected erythrocytes.

Results: A significant correlation was observed between parasite multiplication rate in 48 hours (PMR) and both vaccine-induced growth-inhibitory activity (Pearson $r = -0.93$ [95% CI: $-1.0, -0.27$] $P = 0.02$) and AMA1 antibody titres in the vaccine group (Pearson $r = -0.93$ [95% CI: $-0.99, -0.25$] $P = 0.02$). However immunisation failed to reduce overall mean PMR in the vaccine group in comparison to the controls (vaccinee 16 fold [95% CI: 12, 22], control 17 fold [CI: 0, 65] $P = 0.70$). Therefore no impact on pre-patent period was observed (vaccine group median 8.5 days [range 7.5–9], control group median 9 days [range 7–9]).

Conclusions: Despite the first observation in human experimental malaria infection of a significant association between vaccine-induced *in vitro* growth inhibitory activity and *in vivo* parasite multiplication rate, this did not translate into any observable clinically relevant vaccine effect in this small group of volunteers.



Drugs tested in this system

Published Studies

- Artemether/lumefantrine
- Sulfadoxine/pyrimethamine
- Mefloquine
- Ferroquine
- Piperaquine
- ACT-451840
- Griseofulvin
- OZ439 (Artefenomel)
- DSM265

Unpublished Studies

- KAE609 (Cipargamin)
- MMV048
- SJ733
- Tafenoquine
- M5717

Does data from human challenge predict outcome of clinical trials in malaria Patients?

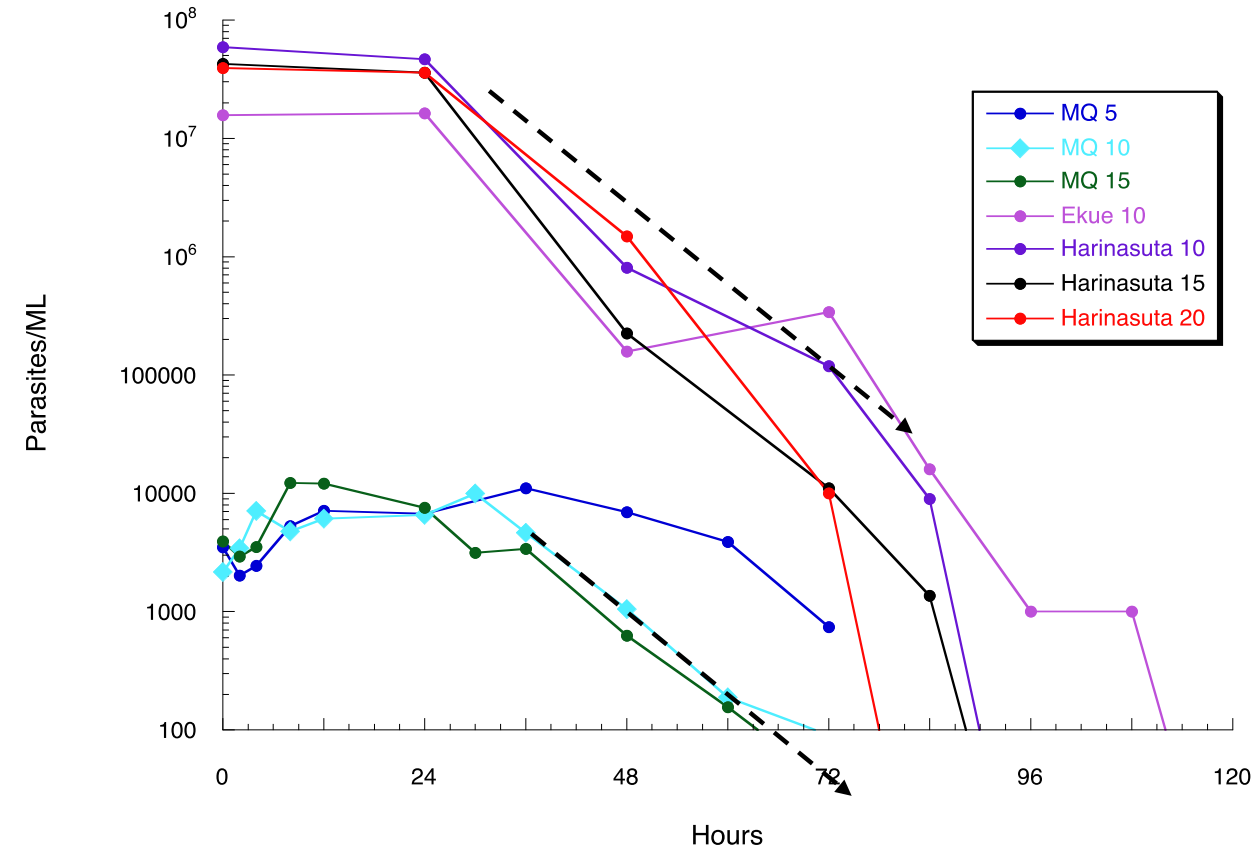
Linking Murine and Human *Plasmodium falciparum* Challenge Models in a Translational Path for Antimalarial Drug Development

James S. McCarthy,^{a,b} Louise Marquart,^a Silvana Sekuloski,^a Katharine Trenholme,^{a,b} Suzanne Elliott,^c Paul Griffin,^{a,b,c,d} Rebecca Rockett,^{b,e} Peter O'Rourke,^a Theo Sloots,^{b,g} Iñigo Angulo-Barturen,^f Santiago Ferrer,^f María Belén Jiménez-Díaz,^f María-Santos Martínez,^f Rob Hooft van Huijsdijnen,^g Stephan Duparc,^g Didier Leroy,^g Timothy N. C. Wells,^g Mark Baker,^{g*} Jörg J. Möhrle^g

QIMR Berghofer Medical Research Institute, Brisbane, Australia^a; University of Queensland, Brisbane, Australia^b; QPharm Pty. Ltd., Brisbane, Australia^c; Mater Health Services, Brisbane, Australia^d; Queensland Paediatric Infectious Diseases (QPID), Herston, Australia^e; GlaxoSmithKline, Tres Cantos Drug Development Campus, Diseases of the Developing World, Tres Cantos, Spain^f; Medicines for Malaria Venture, Geneva, Switzerland^g

Effective progression of candidate antimalarials is dependent on optimal dosing in clinical studies, which is determined by a sound understanding of pharmacokinetics and pharmacodynamics (PK/PD). Recently, two important translational models for antimalarials have been developed: the NOD/SCID/IL2R $\gamma^{-/-}$ (NSG) model, whereby mice are engrafted with noninfected and *Plasmodium falciparum*-infected human erythrocytes, and the induced blood-stage malaria (IBSM) model in human volunteers. The antimalarial mefloquine was used to directly measure the PK/PD in both models, which were compared to previously published trial data for malaria patients. The clinical part was a single-center, controlled study using a blood-stage *Plasmodium falciparum* challenge inoculum in volunteers to characterize the effectiveness of mefloquine against early malaria. The study was conducted in three cohorts ($n = 8$ each) using different doses of mefloquine. The characteristic delay in onset of action of about 24 h was seen in both NSG and IBSM systems. *In vivo* 50% inhibitory concentrations (IC₅₀s) were estimated at 2.0 $\mu\text{g/ml}$ and 1.8 $\mu\text{g/ml}$ in the NSG and IBSM models, respectively, aligning with 1.8 $\mu\text{g/ml}$ reported previously for patients. In the IBSM model, the parasite reduction ratios were 157 and 195 for the 10- and 15-mg/kg doses, within the range of previously reported clinical data for patients but significantly lower than observed in the mouse model. Linking mouse and human challenge models to clinical trial data can accelerate the accrual of critical data on antimalarial drug activity. Such data can guide large clinical trials required for development of urgently needed novel antimalarial combinations. (This trial was registered at the Australian New Zealand Clinical Trials Registry [<http://anzctr.org.au>] under registration number ACTRN12612000323820.)

Antimicrobial Agents and Chemotherapy June 2016 Volume 60 Number 6



- Defined dose response
- Linking of PD backwards to SCID model and forwards to published Phase II data

Efficacy of OZ439 (artefenomel) against early *Plasmodium falciparum* blood-stage malaria infection in healthy volunteers

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Objectives: OZ439, or artefenomel, is an investigational synthetic ozonide antimalarial with similar potency, but a significantly improved pharmacokinetic profile, compared with artemisinins. We wished to measure key pharmacokinetic and pharmacodynamic parameters and the pharmacokinetic/pharmacodynamic relationship of artefenomel in humans to guide the drug's further development as combination therapy in patients.

Patients and methods: We tested artefenomel in the human induced blood-stage malaria (IBSM) model. *Plasmodium* infection was monitored by quantitative PCR (qPCR) and upon reaching 1000 parasites/mL single doses of 100, 200 and 500 mg of artefenomel were administered orally with evaluation of drug exposure and parasitaemia until rescue treatment after 16 days or earlier, if required.

Results: A single 100 mg dose had only a transient effect, while the 200 mg dose resulted in a significant reduction in parasitaemia before early recrudescence. At the highest (500 mg) dose, initial clearance of parasites below the limit of detection of qPCR was observed, with a 48 h parasite reduction ratio (PRR₄₈) >10000 and a parasite clearance half-life of 3.6 h (95% CI 3.4–3.8 h). However, at this dose, recrudescence was seen in four of eight subjects 6–10 days after treatment. Pharmacokinetic/pharmacodynamic modelling predicted an MIC of 4.1 ng/mL.

Conclusions: These results confirm the antimalarial potential of artefenomel for use in a single-exposure combination therapy. The observations from this study support and will assist further clinical development of artefenomel.

J Antimicrob Chemother 2016; **71**: 2620–2627

- Single dose 100, 200 and 500 mg
- Follow up to SD16
- At 500 mg:
 - PRR₄₈ >4
 - Parasite clearance t_{1/2} 3.6 hr
 - MIC: 4.1 ng/ml

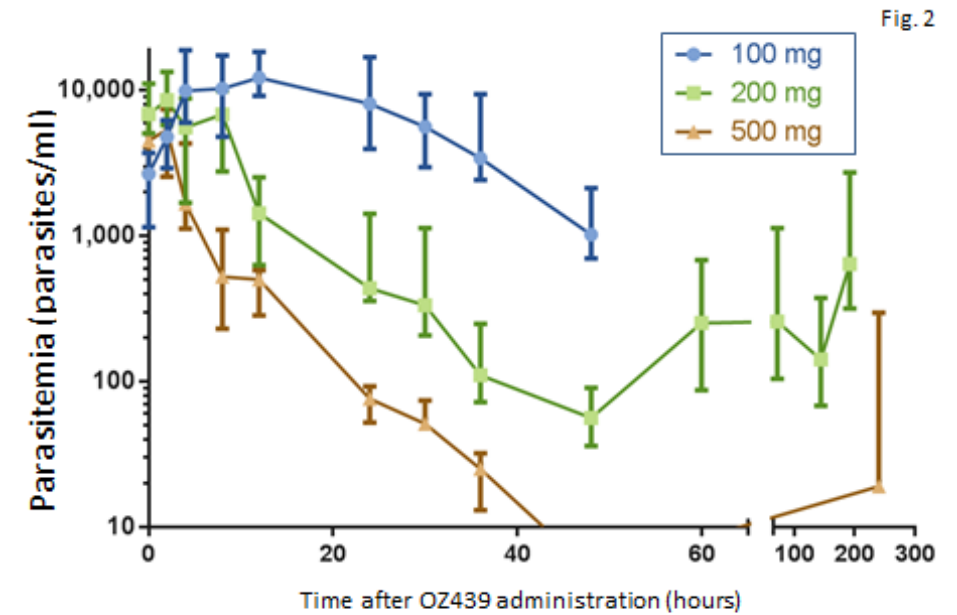
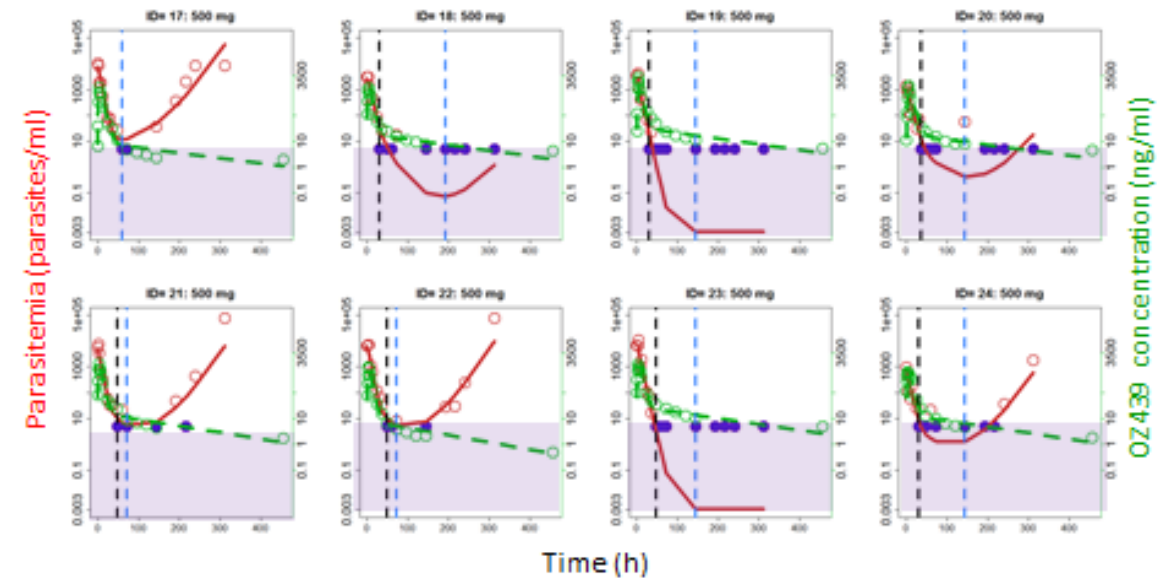


Fig. 2



A Phase II pilot trial to evaluate safety and efficacy of ferroquine against early *Plasmodium falciparum* in an induced blood-stage malaria infection study

Malaria Journal

James S. McCarthy^{1,2}, Thomas Rückle³, Elhadj Djeriou⁴, Cathy Cantalloube⁸, Daniel Ter-Minassian⁴, Mark Baker^{3,7}, Peter O'Rourke¹, Paul Griffin^{1,2,5,6}, Louise Marquart¹, Rob Hooft van Huijsduijnen³ and Jörg J. Möhrle^{3*}

Abstract

Background: Ferroquine (SSR97193) is a candidate anti-malarial currently undergoing clinical trials for malaria. To better understand its pharmacokinetic (PK) and pharmacodynamic (PD) parameters the compound was tested in the experimentally induced blood stage malaria infection model in volunteers.

Methods: Male and non-pregnant female aged 18–50 years were screened for this phase II, controlled, single-centre clinical trial. Subjects were inoculated with ~1800 viable *Plasmodium falciparum* 3D7A-infected human erythrocytes, and treated with a single-dose of 800 mg ferroquine. Blood samples were taken at defined time-points to measure PK and PD parameters. The blood concentration of ferroquine and its active metabolite, SSR97213, were measured on dry blood spot samples by ultra-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS). Parasitaemia and emergence of gametocytes were monitored by quantitative PCR. Safety was determined by recording adverse events and monitoring clinical laboratory assessments during the course of the study.

Results: Eight subjects were enrolled into the study, inoculated with infected erythrocytes and treated with 800 mg ferroquine. Ferroquine was rapidly absorbed with maximal exposure after 4–8 and 4–12 h exposure for SSR97213. Non-compartmental PK analysis resulted in estimates for half-lives of 10.9 and 23.8 days for ferroquine and SSR97213, respectively. Parasite clearance as reported by parasite reduction ratio was 162.9 (95 % CI 141–188) corresponding to a parasite clearance half-life of 6.5 h (95 % CI: 6.4–6.7 h). PK/PD modelling resulted in a predicted minimal parasitocidal concentration of 20 ng/mL, and the single dosing tested in this study was predicted to maintain an exposure above this threshold for 454 h (37.8 days). Although ferroquine was overall well tolerated, transient elevated transaminase levels were observed in three subjects. Paracetamol was the only concomitant treatment among the two out of these three subjects that may have played a role in the elevated transaminases levels. No clinically significant ECG abnormalities were observed.

Conclusions: The parameters and PK/PD model derived from this study pave the way to the further rational development of ferroquine as an anti-malarial partner drug. The safety of ferroquine has to be further explored in controlled human trials.

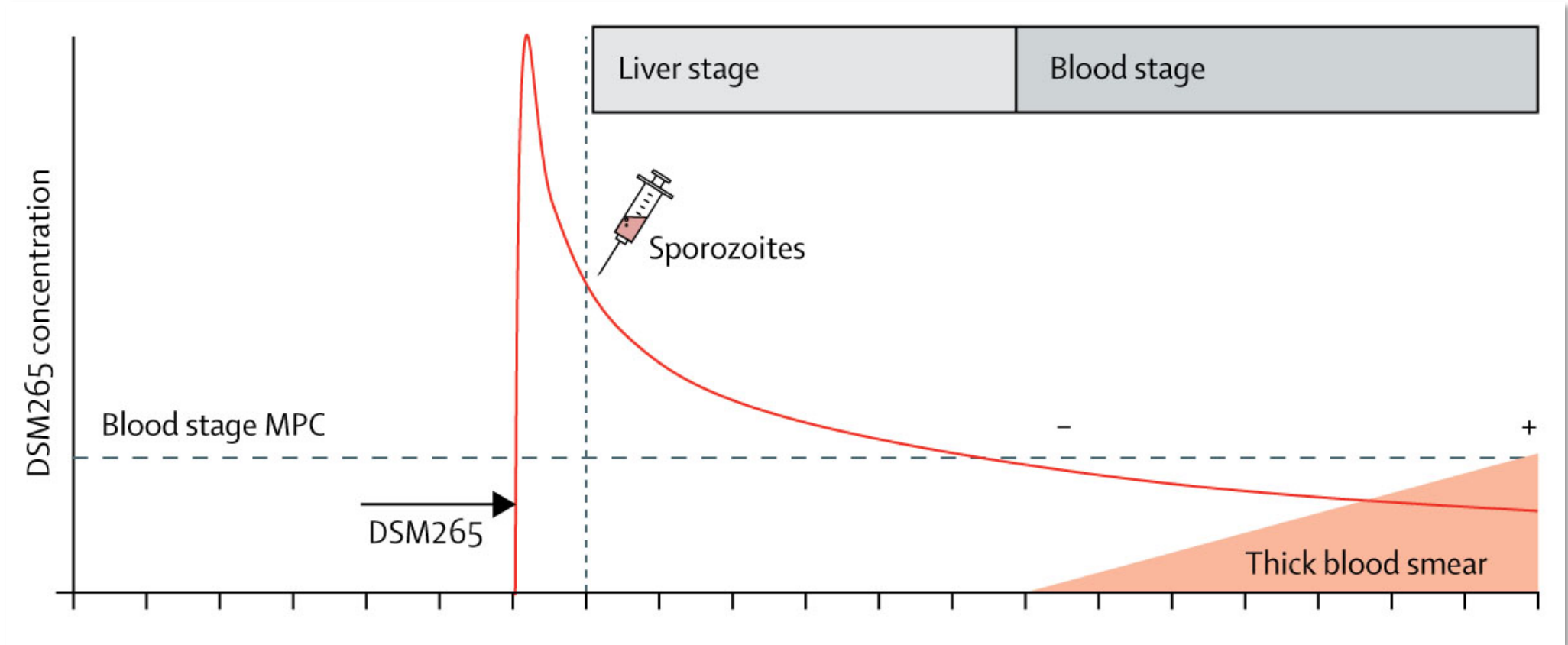
Malar J (2016) 15:469

Ferroquine

- Determine MIC with a single cohort
- Guide dose selection for IIb study[†]

† Evaluate the Efficacy of a Single Dose Regimen of Ferroquine and Artefenomel in Adults and Children With Uncomplicated *P. falciparum* Malaria
ClinicalTrials.gov: NCT02497612

Challenge studies to investigate antimalarial activity in the liver



Conclusions

- SCID Mouse and human challenge models provide useful platforms to gain key efficacy data on investigational antimalarials
- They provide key data for pharmacometric analysis

Future Prospects

- Adapt the models to test combinations of antimalarials
- Other lifecycle stages (eg transmission blocking)
- New parasite strains and species (Drug-resistant parasites, *P. vivax*)

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QIMR Berghofer

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MMV - Stephan Chalon, Nathalie Gobeau, Joerg Moehrle, Jeremy Burrows, Tim Wells



The volunteers

