Clinical Development of New Antimalarials

Accelerating Early Development of P218 through CHMI Models

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10th NSTDA Annual Conference - Bangkok, March 31st 2017

Defeating Malaria Together

MMV
Medicines for Malaria Venture

MMV Team in 2017

Supporting discovery, development & delivery of new antimalarials

A foundation of 60 people working towards the same mission, to reduce the burden of malaria in disease-endemic countries by

DISCOVERING, DEVELOPING and DELIVERING new, effective and affordable antimalarial drugs

A Global Product Development Partnership

More than 400 partners spanning the World

- 61 pharmaceuticals companies
- 21 biotech companies
- 146 research and academic institutes
- 109 clinical centres
- 45 NGOs, not-for-profits and intl orgs
- 43 governments

Malaria in 2017

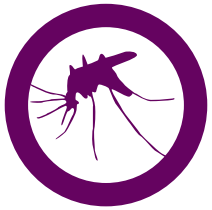
Unmet medical needs

RESISTANCE

CHILDREN & PREGNANT WOMEN

SINGLE DOSE CURES

PREVENTION OF RELAPSE



TRANSMISSION BLOCKING

CHEMO PREVENTION

Malaria in 2017

Unmet medical needs – P218 fit

RESISTANCE

SP resistance (IPTp; SMC)

CHILDREN & PREGNANT WOMEN

Safe chemo-protection for pregnant women

1x

SINGLE DOSE CURES

PREVENTION OF RELAPSE

TRANSMISSION BLOCKING

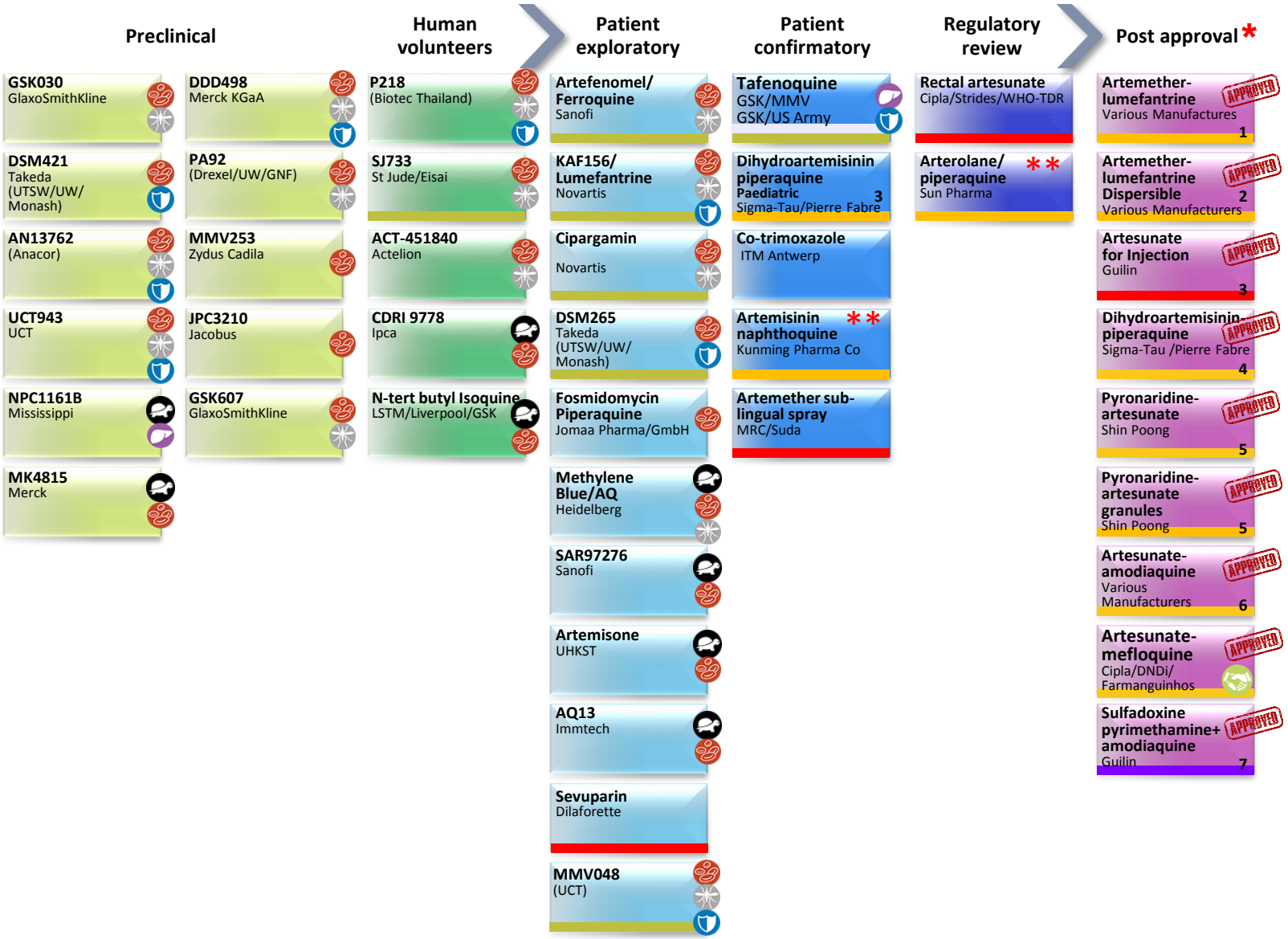
CHEMO PREVENTION

Good safety & tolerability

Weekly or monthly treatment

Malaria : Global Portfolio (Q4-2016)

27 Projects in T-Med & Early Development Stage



Malaria : Global Portfolio

Footnotes

Target Product Profiles and Target Candidate Profiles

MMV has defined Target Product Profiles and Target Candidate Profiles for medicines to support the eradication campaign. Burrows J et al.; Designing the next generation of medicines for malaria control. *Malaria Journal* 2013 12:187, which is being updated for publication in 2017

Target Product Profiles
indicated by bars at the bottom of each compound box

- 3-day cure, artemisinin-based combination therapies
- Combinations aiming at a new Single exposure radical cure (TPP-1)
- Severe malaria and pre-referral treatment
- Intermittent /Seasonal Malaria Chemoprevention
- Products targeting prevention of relapse for *P. vivax*
- There are currently no products in the development portfolio meeting the Single Exposure Chemoprotection (SEC) TPP-2

Footnote for Generic names on Global Portfolio

1. First approval: Novartis (Brand name: Coartem®). Generics by Ajanta, Cipla, Ipca, Strides, Macleods, Mylan;
2. First approval: Novartis (Brand name: Coartem® *Dispersible*). Generic by Ajanta;
3. Brand name: Artesun®;
4. Brand name: Eurartesim®;
5. Brand name: Pyramax® Tablets and Granules;
6. First approval fixed-dose combination: Sanofi/DNDi (Brand name: ASAQ Winthrop). Generics by Ajanta, Cipla, Guilin, Ipca, Strides;
7. Brand name: SPAQ-CO™;

Target Candidate Profiles
activities for each individual molecule, indicated by symbols added to each compound in the translational portfolio

	Burrows et al., 2013	Burrows et al., 2017
Asexual blood stages	(TCP-1,2)	TCP-1
Relapse prevention	(TCP-3a)	TCP-3
Transmission reduction	(TCP-3b)	TCP-5
Chemoprevention	(TCP- 4)	TCP-4

Additional Symbols on Global Portfolio

- Brought into portfolio after approval; collaborations with DNDi
- No progress report in the last two years
- * Pending review or approval by WHO pre-qualification, or by regulatory bodies who are ICH members or observers
- ** Approved in several countries but not approved by WHO pre-qualification nor regulatory bodies who are ICH members or observers

Malaria : Global Portfolio (2017)

9 New Chemical Entities in Clinical Development

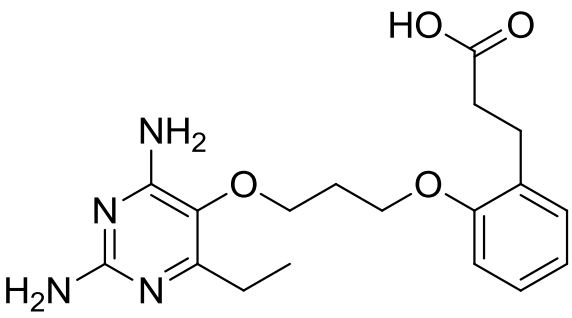
Eurartesim-dispersible (Phase III)
Tafenoquine (Phase III)
OZ439+feroquine (Phase IIb)
KAE609 (Phase IIa)
KAF156 (Phase IIa)
DSM265 (Phase IIa)
MMV048 (Phase I)
SJ733 St. Jude/Eisai (Phase I)
P218 Biotec (Phase I)

P218 – A New DHFR Inhibitor

Primary target indication = chemoprotection

P218

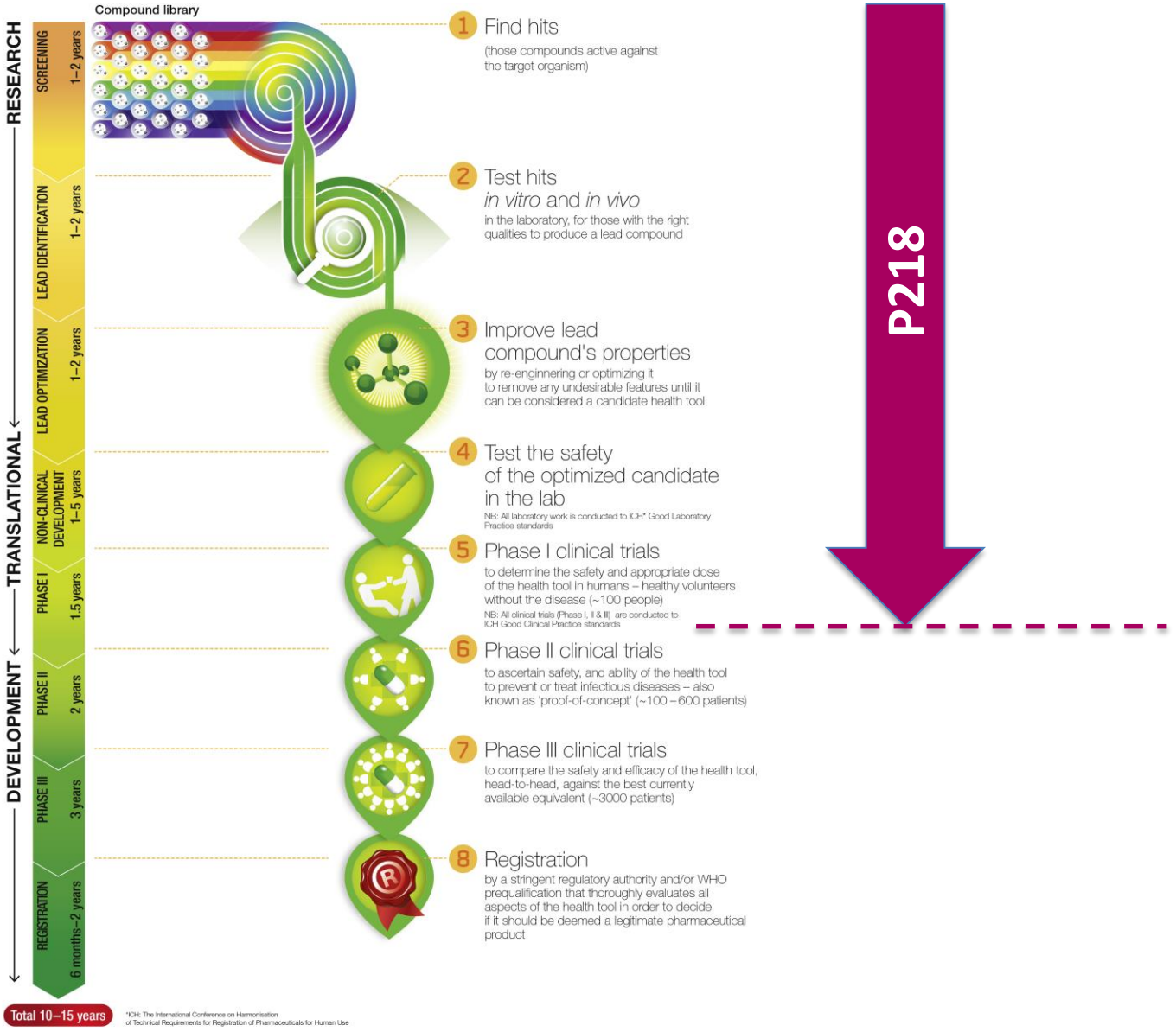
(BIOTEC Thailand)



Product vision	• Potential for Chemoprotection
MoA	• *P. falciparum* dihydrofolate reductase (DHFR) inhibitor
Key features	• Clinically validated pathway • Activity against wild type, and antifolate resistance-conferring quadruple mutants
Challenges	• 10 fold difference between *P. falciparum* and *P. vivax* IC50 in *ex-vivo* field isolates
Status	• First in human study ongoing
Next milestone	• Go/no go decision to initiate controlled human malaria infection cohort
MMV Project Director	• Dr Emilie Rossignol

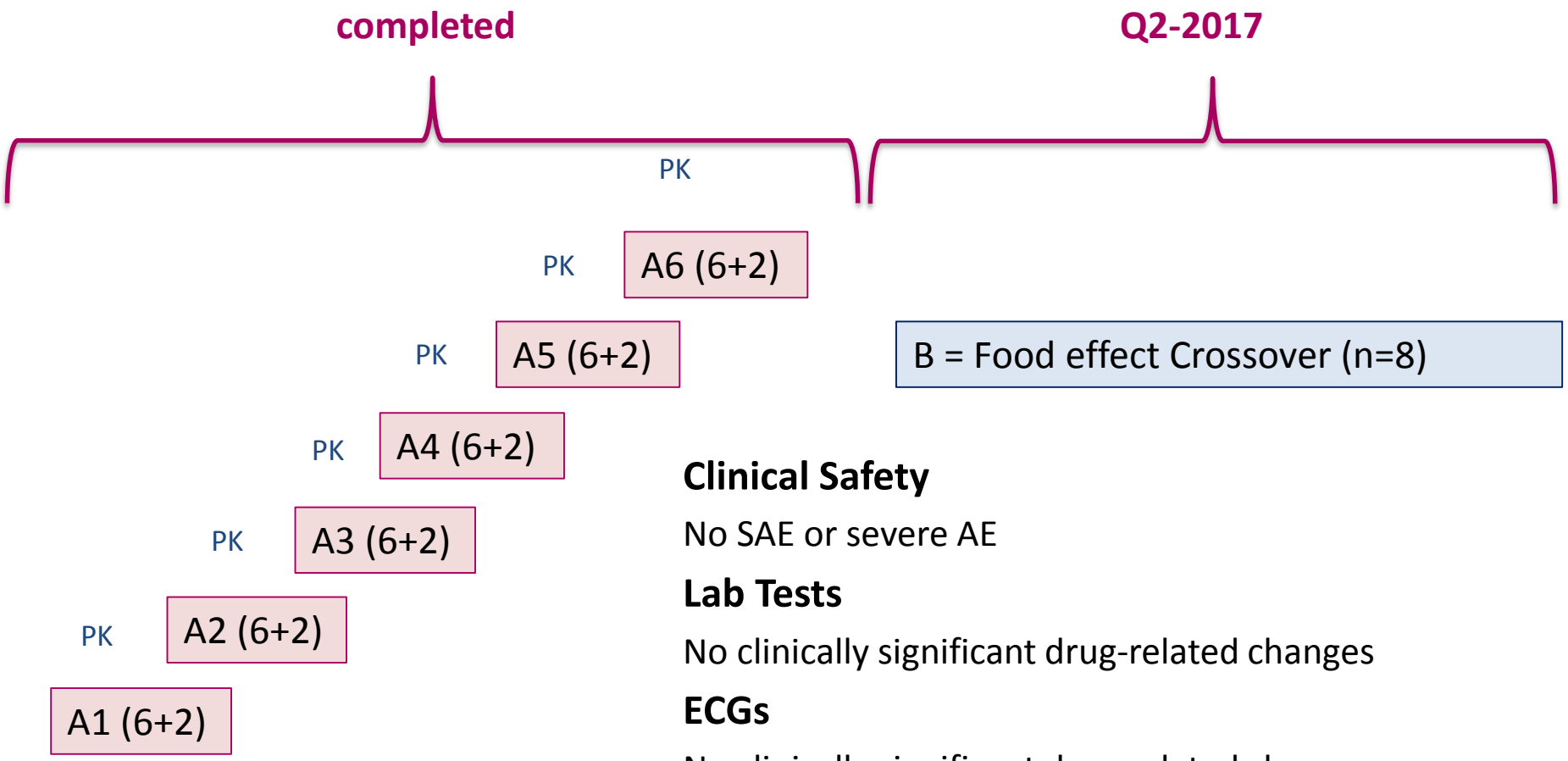
P218 – A New DHFR Inhibitor

Current status = Phase 1 studies / Healthy subjects



FIM Study with P218

10 -750mg (Ongoing study, London, UK) – Preliminary results



Clinical Safety

No SAE or severe AE

Lab Tests

No clinically significant drug-related changes

ECGs

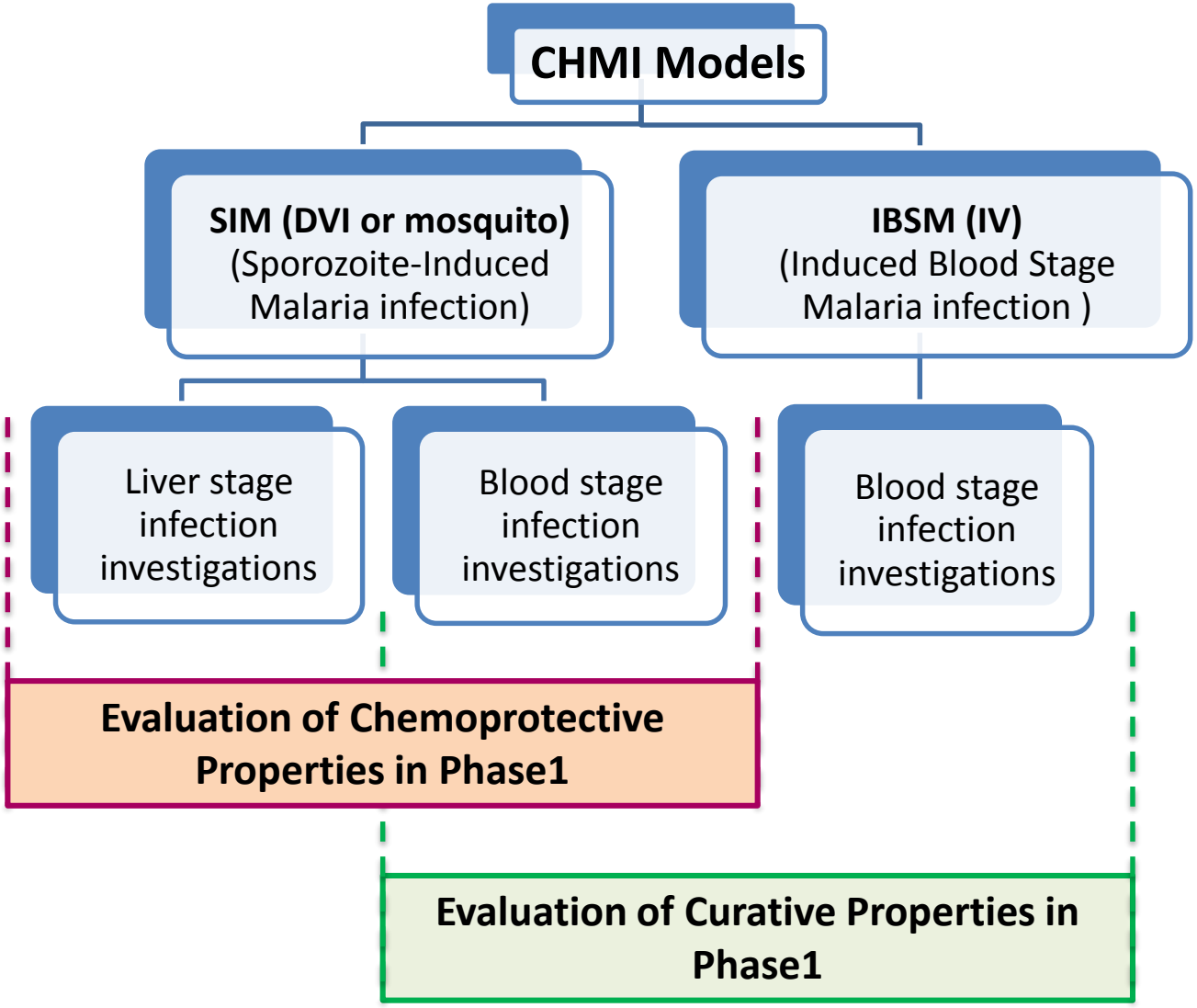
No clinically significant drug-related changes

Pharmacokinetics

Acceptable PK variability, dose-proportionality

Controlled Human Malaria Infection

For early evaluation of NCEs : sporozoite & blood stage models

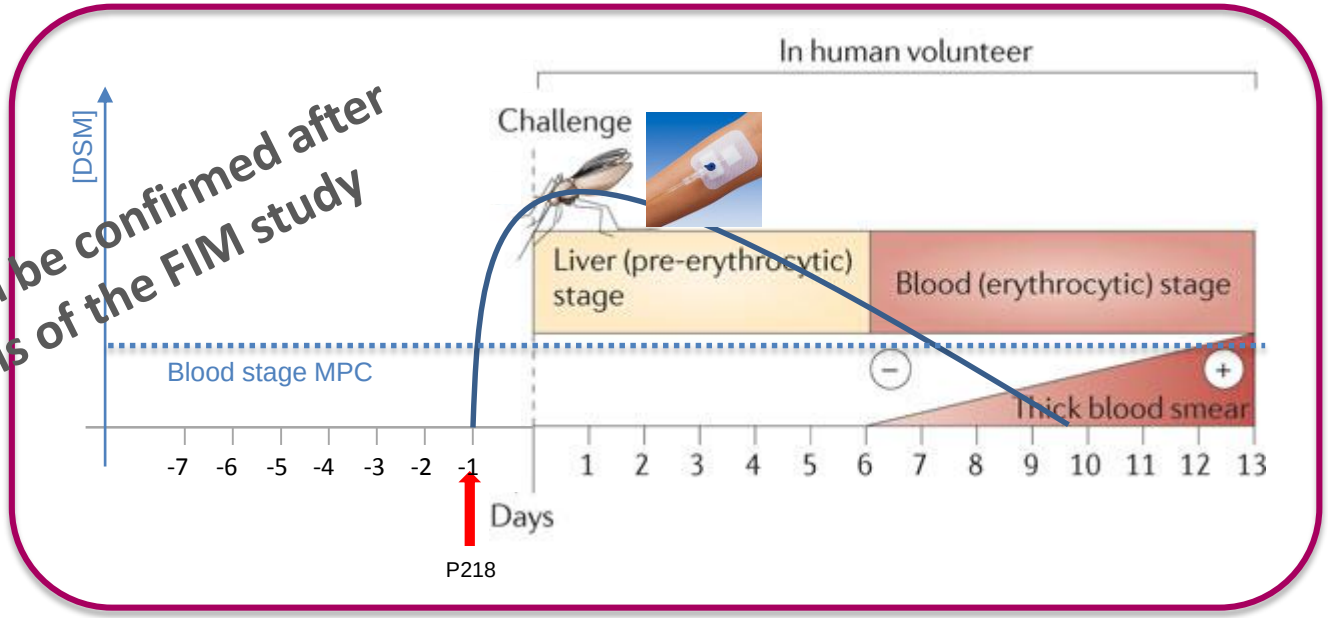


Controlled Human Malaria Infection

Next study with P218 = Sporozoite (DVI) model

P218 (Regimen TBD based on FIM data) on Day -1

- Drug exposure covers liver stage and early blood stage until MPC
- Chemoprophylactic activity is causal and suppressive



Design will be confirmed after analysis of the FIM study

If chemoprotection is achieved with dosing on Day -1

- Increase interval with administration of P218 on Day -X

Controlled Human Malaria Infection

Example of MMV Sporozoite Challenge Study : DSM265

DSM265 for *Plasmodium falciparum* chemoprophylaxis: a randomised, double blinded, phase 1 trial with controlled human malaria infection

Mihály Sulyok, Thomas Rückle, Alexandra Roth, Raymund E Mürbeth, Stephan Chalon, Nicola Kerr, Sonia Schnieper Samec, Nathalie Gobeau, Carlos Lamsfus Calle, Javier Ibáñez, Zita Sulyok, Jana Held, Tamirat Gebru, Patricia Granados, Sina Brückner, Christian Nguetse, Juliana Mengue, Albert Lalremruata, Kim Lee Sim, Stephen L Hoffman, Jörg J Möhrle, Peter G Kremsner, Benjamin Mordmüller**

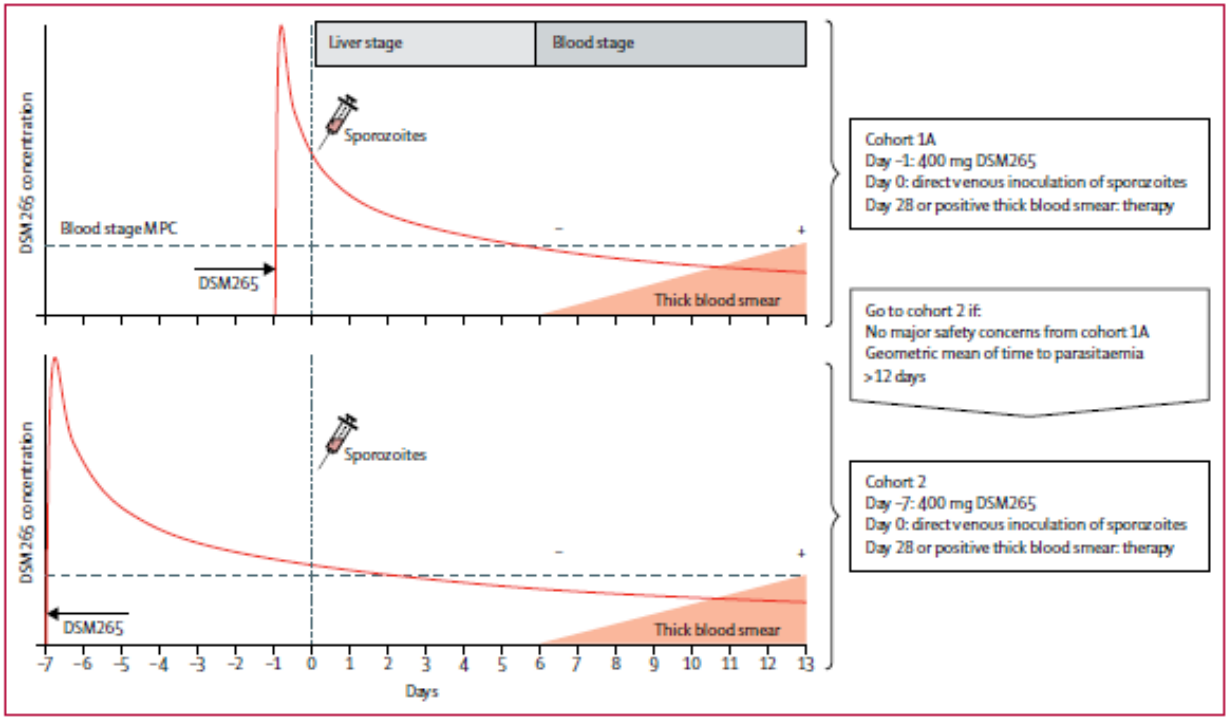


Figure 1: Study design and main interventions
Red curves show the expected DSM265 concentrations. MPC=minimal parasiticidal concentration.

www.thelancet.com/infection Published online March 28, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30139-1

Controlled Human Malaria Infection

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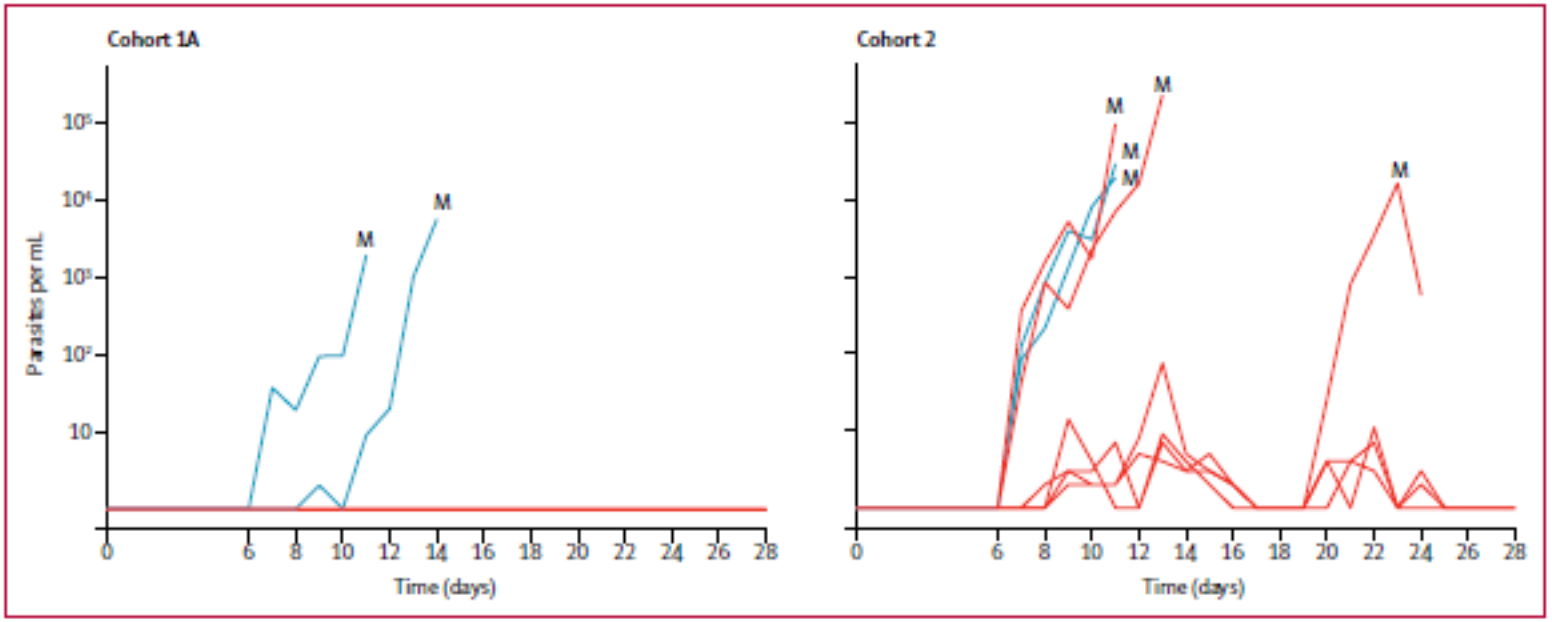

Figure 3: Parasitaemia assessed by quantitative PCR
Placebo volunteers (blue) and DSM265 volunteers (red). In cohort 1A, all DSM265 volunteers remained negative, in cohort 2 all became positive. M=malaria defined as positive thick blood smear.

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Acknowledgements

Collaboration Biotec – NSTDA - MMV

Biotec

- *Y. Yuthavong*
- S. Kamchonwongpaisan
- D. Kongkasuriyachai
- B. Tarnchompoo

NSTDA

- M. Thammasatta

MMV – Medical

- *S. Duparc*
- *S. Akakpo*

MMV – TMed

- *G. Langdon*

MMV – Discovery

- *J. Burrows*
- *P. Willis*
- *B. Campo*
- *D. Leroy*