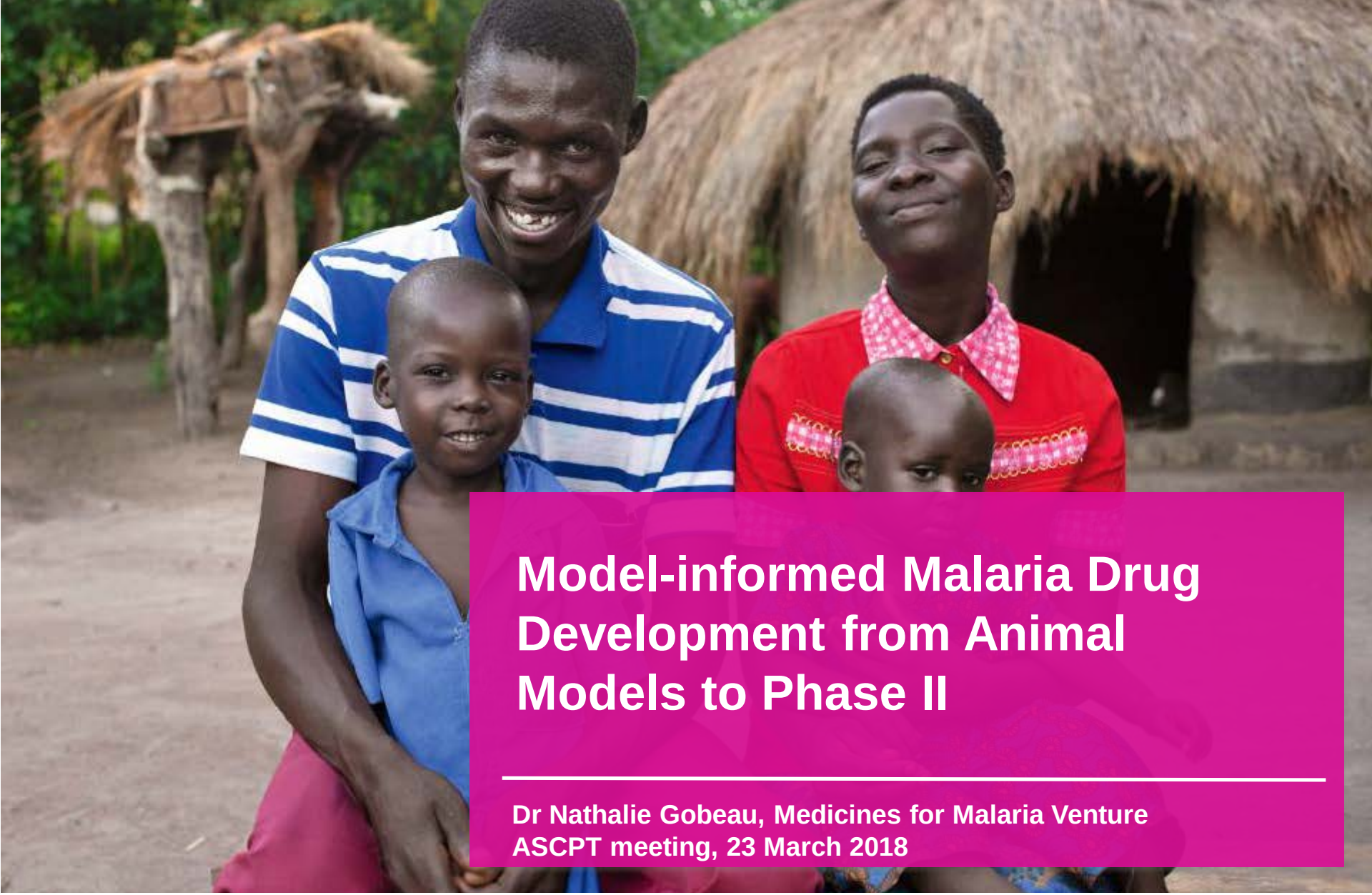

Model-informed Malaria Drug Development from Animal Models to Phase II

Dr Nathalie Gobeau, Medicines for Malaria Venture
ASCPT meeting, 23 March 2018

Defeating Malaria Together

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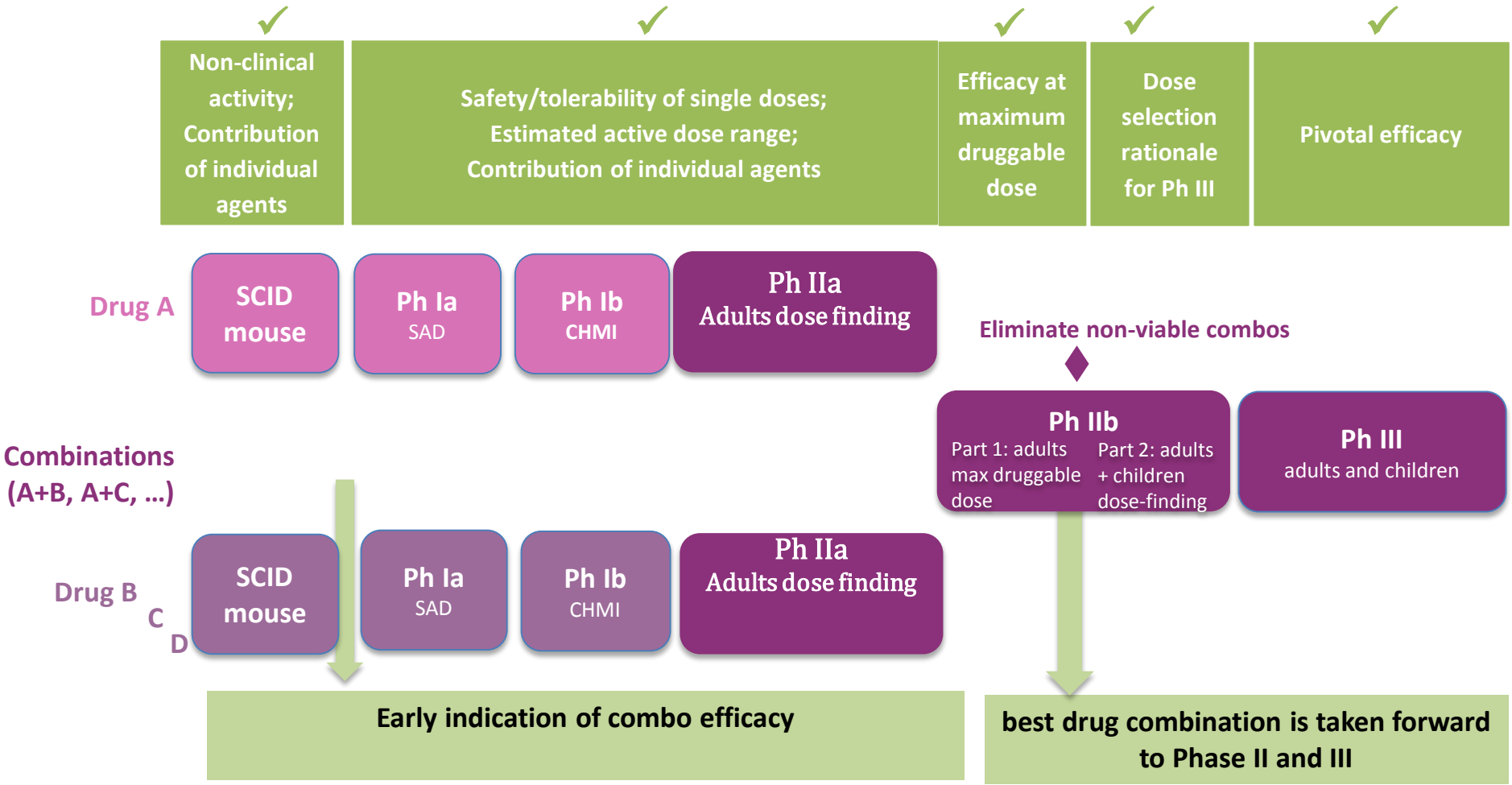
Outline

- **Plan for the development of antimalarial treatment and the role of Modeling & Simulation**
- **Translation of the PKPD relationship across the pharmacological models (mice, challenge volunteers, patients): one example**
- **Conclusion and perspectives**

Current Development Plan for Acute Uncomplicated Malaria



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Computational methods – advanced pharmacometric modeling allows to estimate efficacy before Phase II

First in Human Pharmacokinetics (PK) data (drug concentration vs time)

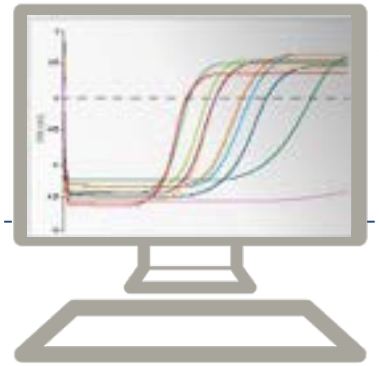
+

In-vitro PK interactions (for combinations)

Controlled Human Malaria Infection (CHMI) model (for combinations)

+

Severe Combined Immuno-Deficiency mouse (SCID) model (for combinations)



Physiologically based pharmacokinetic (PBPK) model: Absorption, distribution, metabolism and excretion prediction for single agents and combinations

Pharmacokinetic/ pharmacodynamic (PK/PD) model: parasitemia and drug concentration vs time

Key insights from pharmacometrics

- **Estimate of drug efficacy** and prediction of in-human dosing and **cure rate**
- **Acceleration of progression from pre-clinical to clinical stages** thanks to ranking of combinations efficacy and early identification of non-viable candidates

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How does PKPD translate across the pharmacology models?

SCID mice
Inoculated blood stage malaria in immunodeficient mice engrafted with human red blood cells

→

CHMI
Induced blood stage malaria in healthy volunteers

→

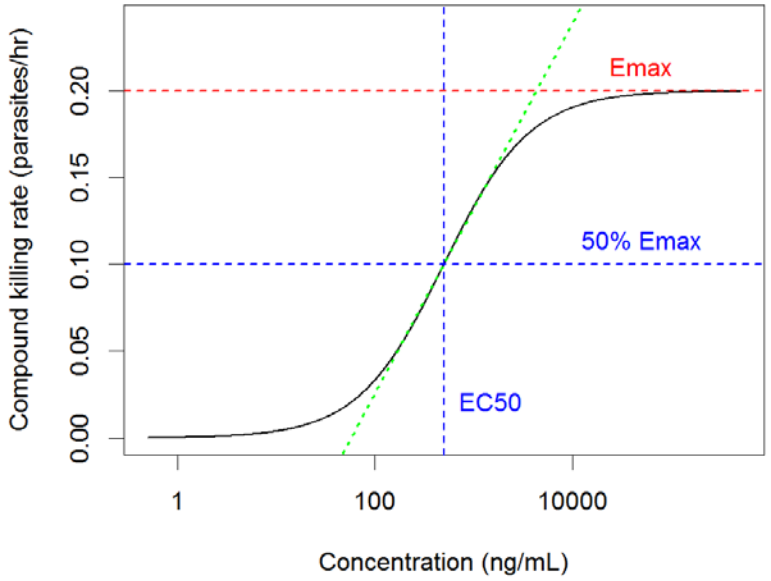
Patients

Measurements

$$Kkill = \frac{E\,max\,C^{Hill}}{EC50^{Hill} + C^{Hill}}$$

PK profile

PD profile

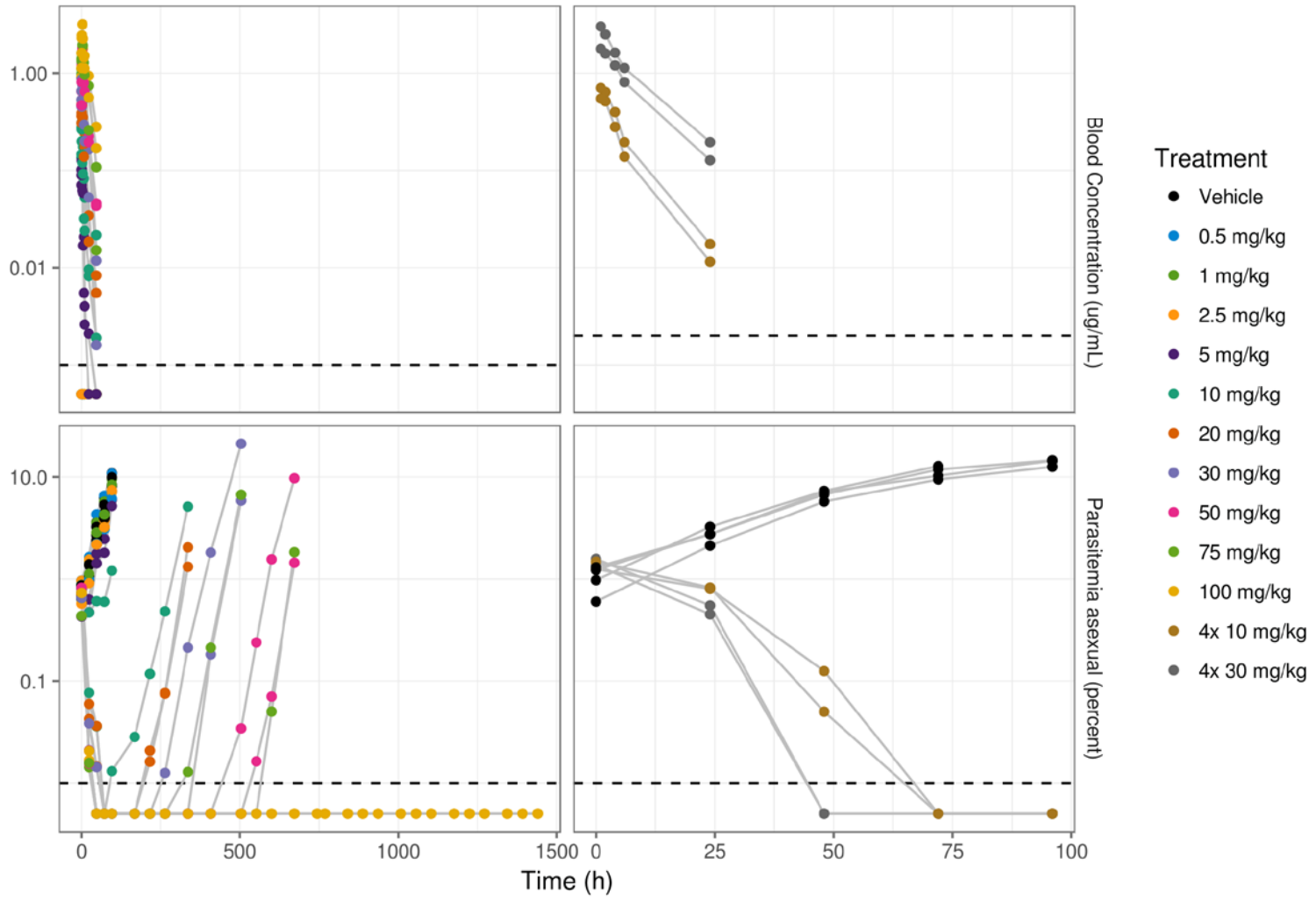


Example: Artefenomel

	SCID mouse	CHMI	Patients
Artefenomel	1 short experiment: • 2 dosing regimens; • over 1 week 1 long experiment: • 10 dosing regimens; • over 4 weeks	100 mg [N=8] 200 mg [N=8] 500 mg [N=8] Over one month	100 mg [N=7] 500 mg [N=15] Over one month

PK and parasitemia are measured in each individual mice and several doses are tested

PK and parasitemia profiles in mice after administration of Artefenomel



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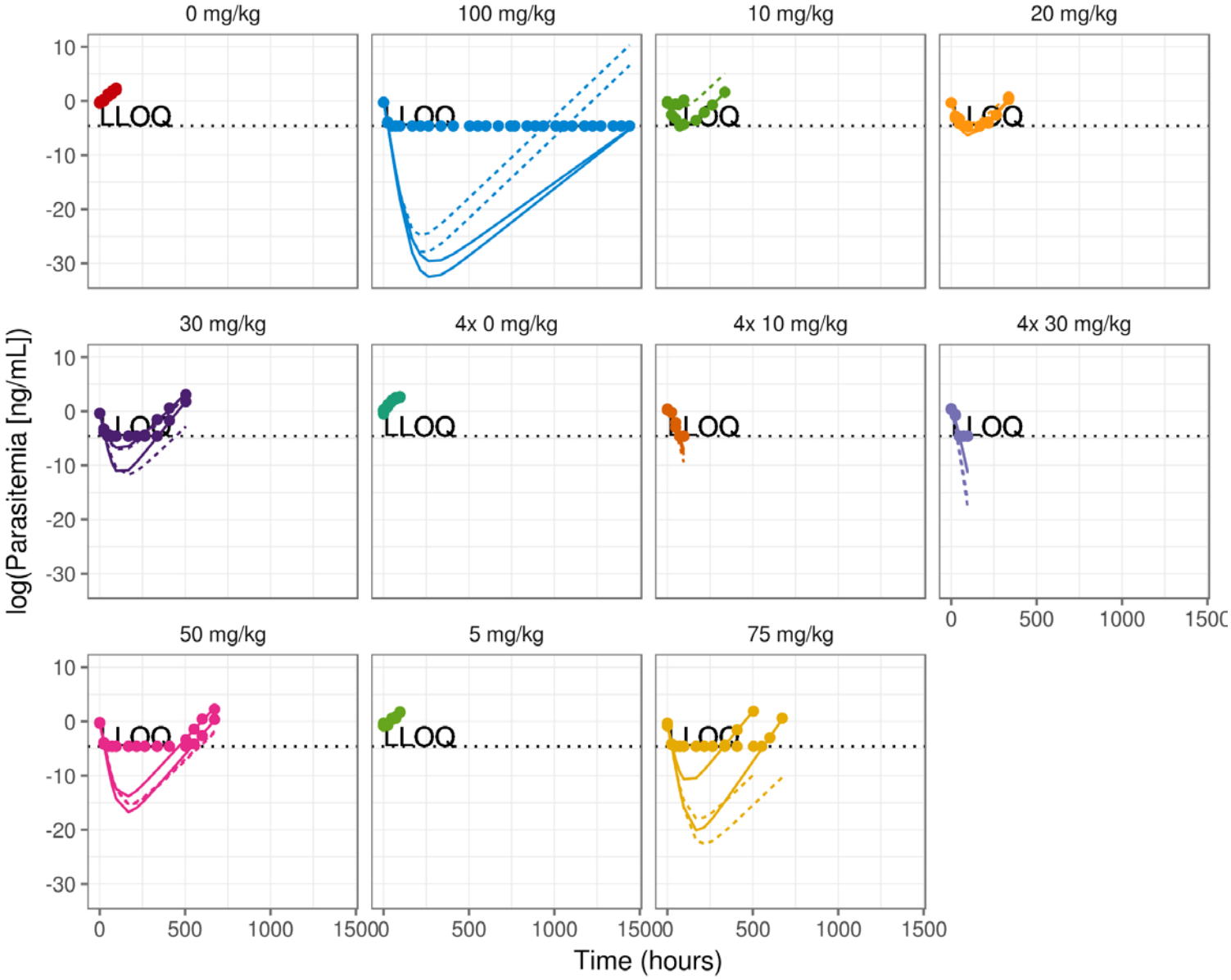
A PKPD model is derived …



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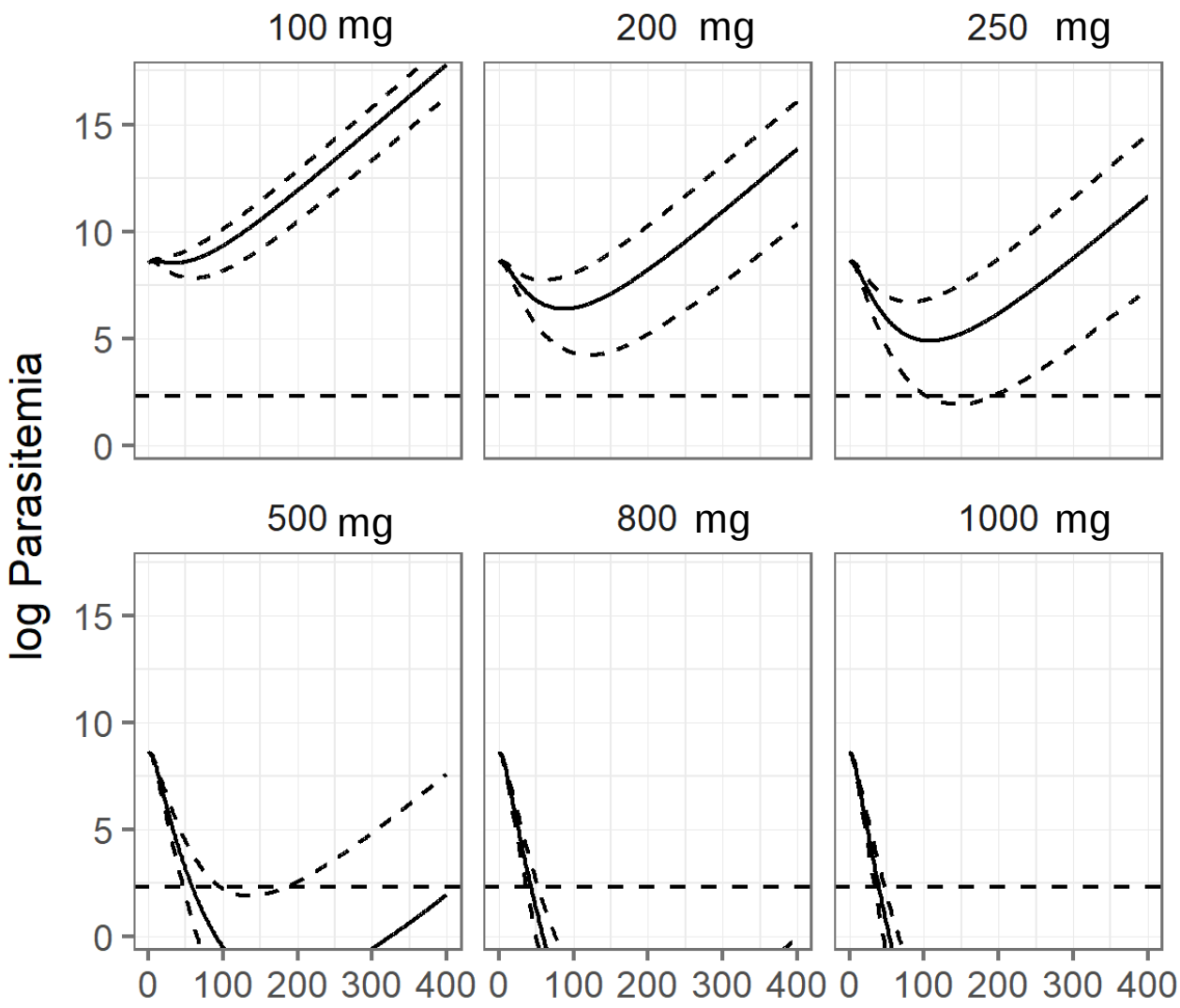
… and used to select the doses in CHMI study

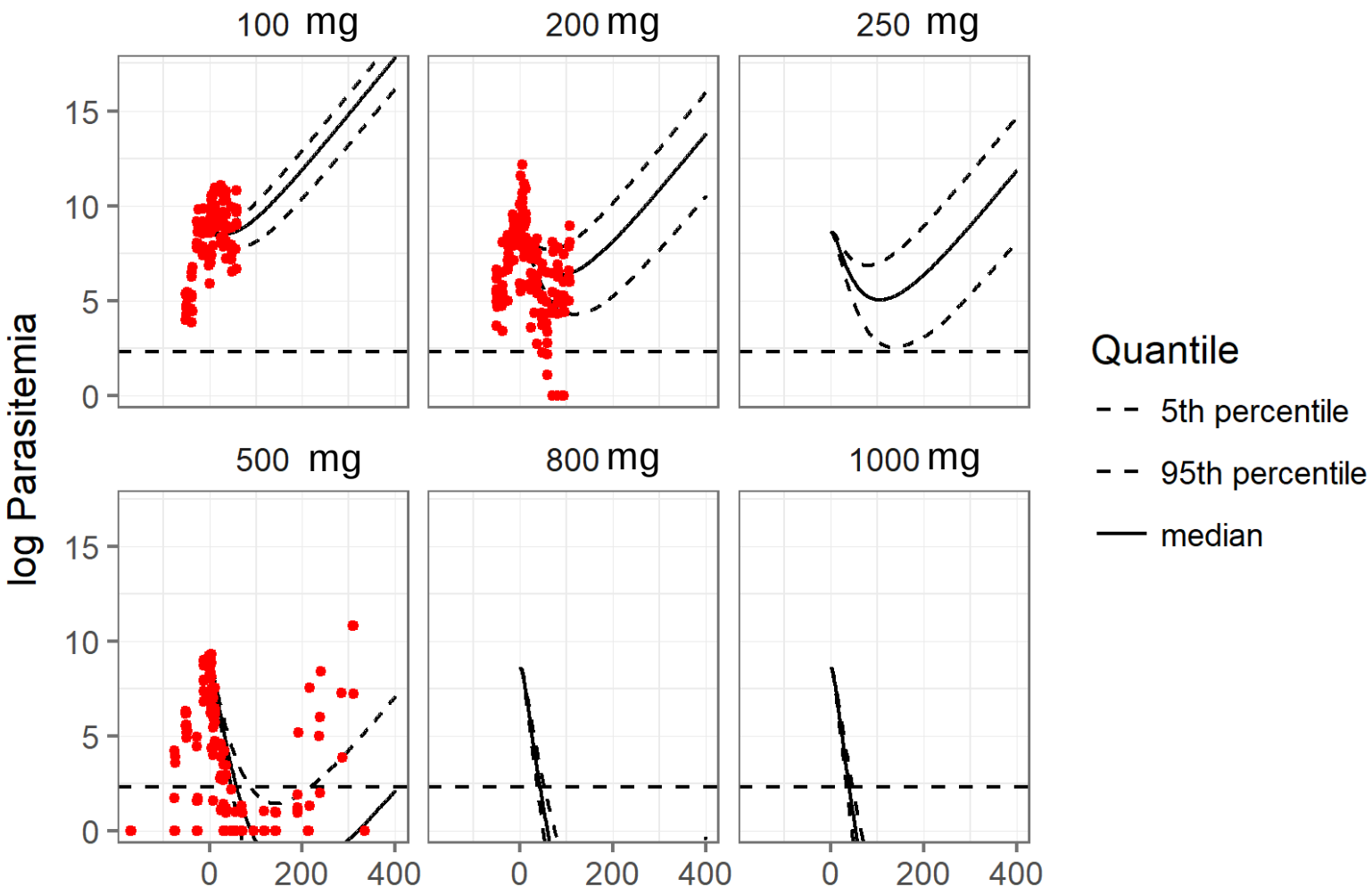


- Population PK from FIH data
- PKPD model from SCID data

Quantile

- - - 5th percentile
- - - 95th percentile
—— median

Compare CHMI predictions with SCID PKPD model and CHMI observations (Artefenomel)



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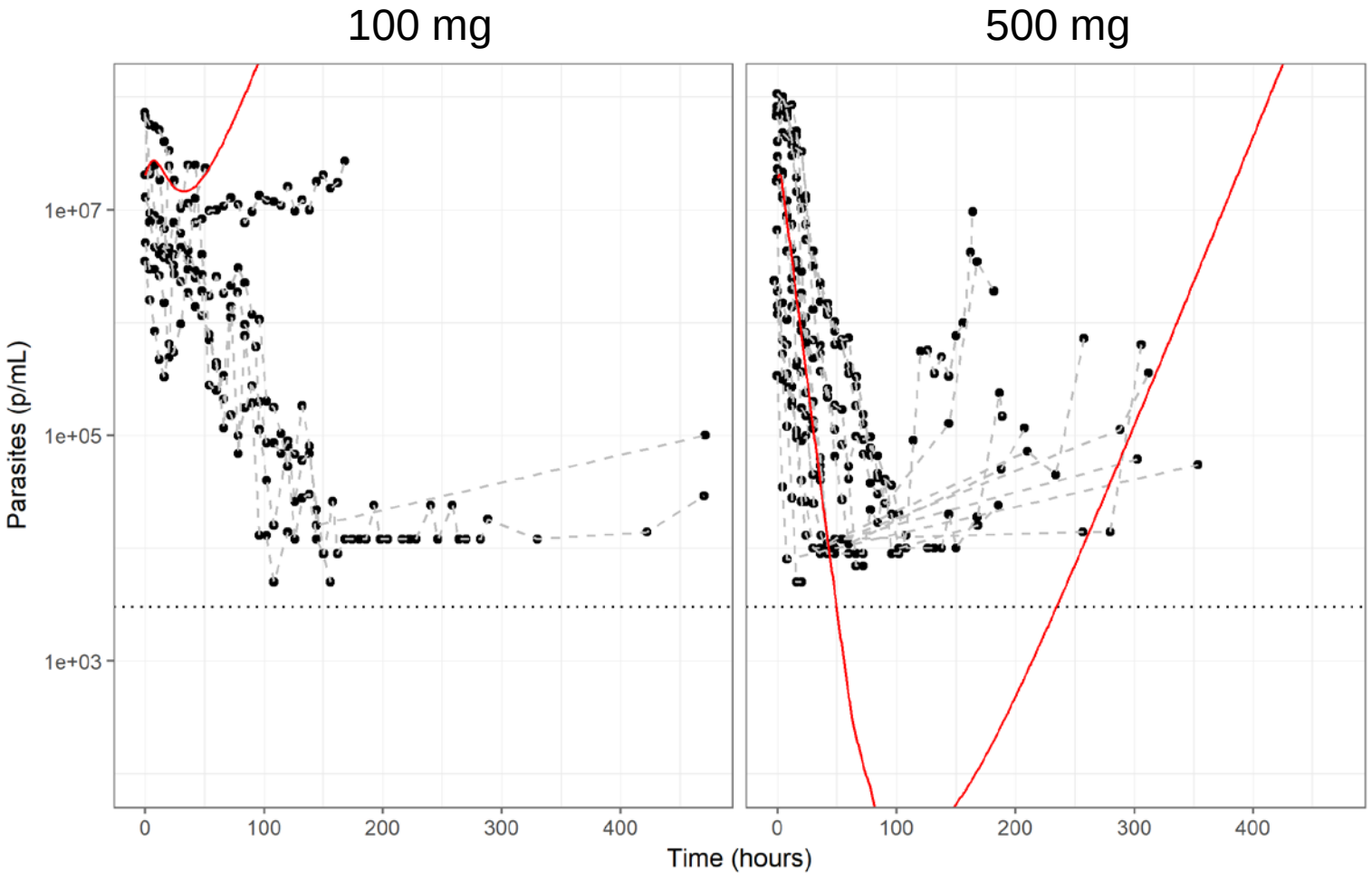
The CHMI PKPD model is then used to predict response in patients with higher baseline parasitemia



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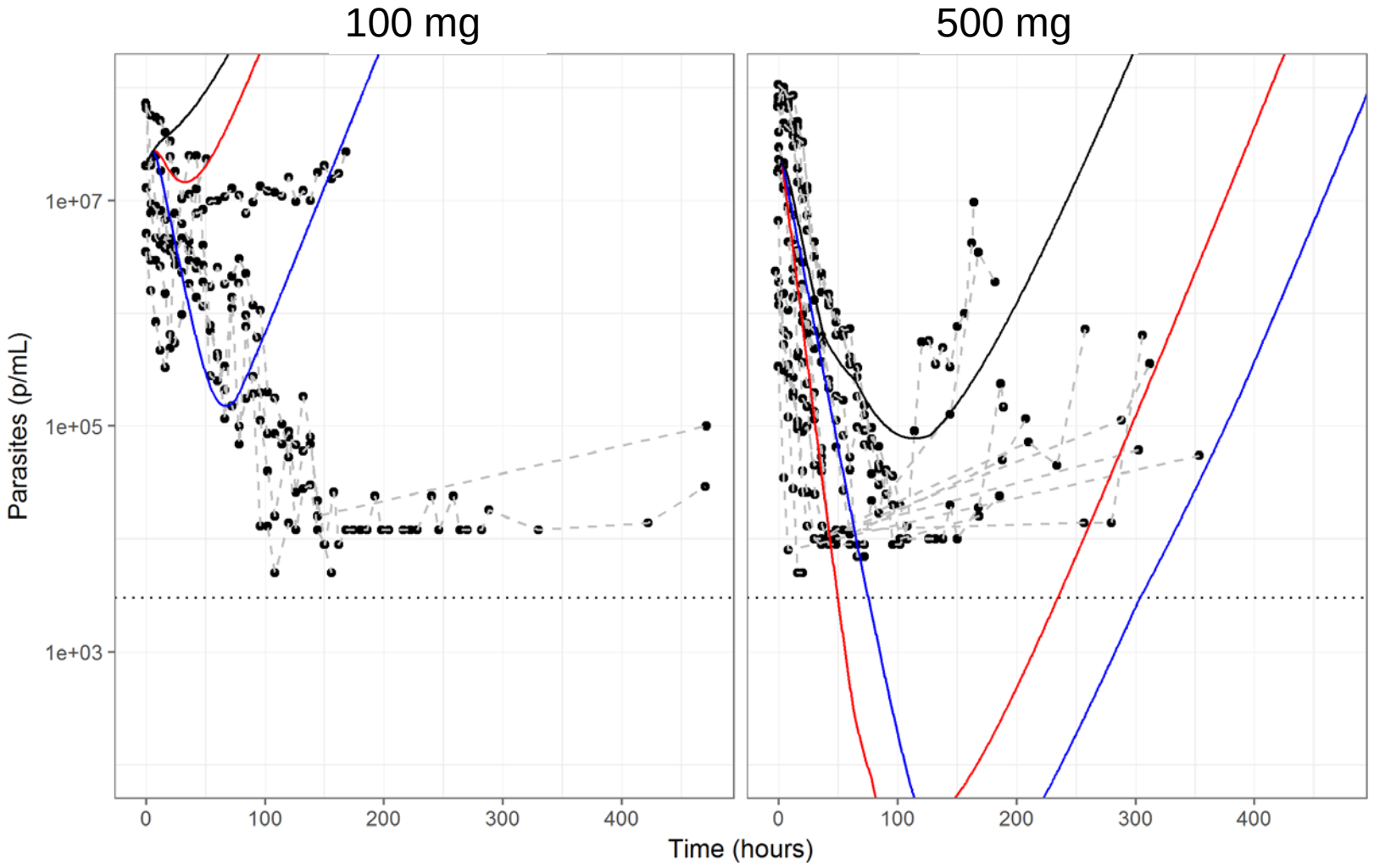
The PKPD model is refined with the observations in patients

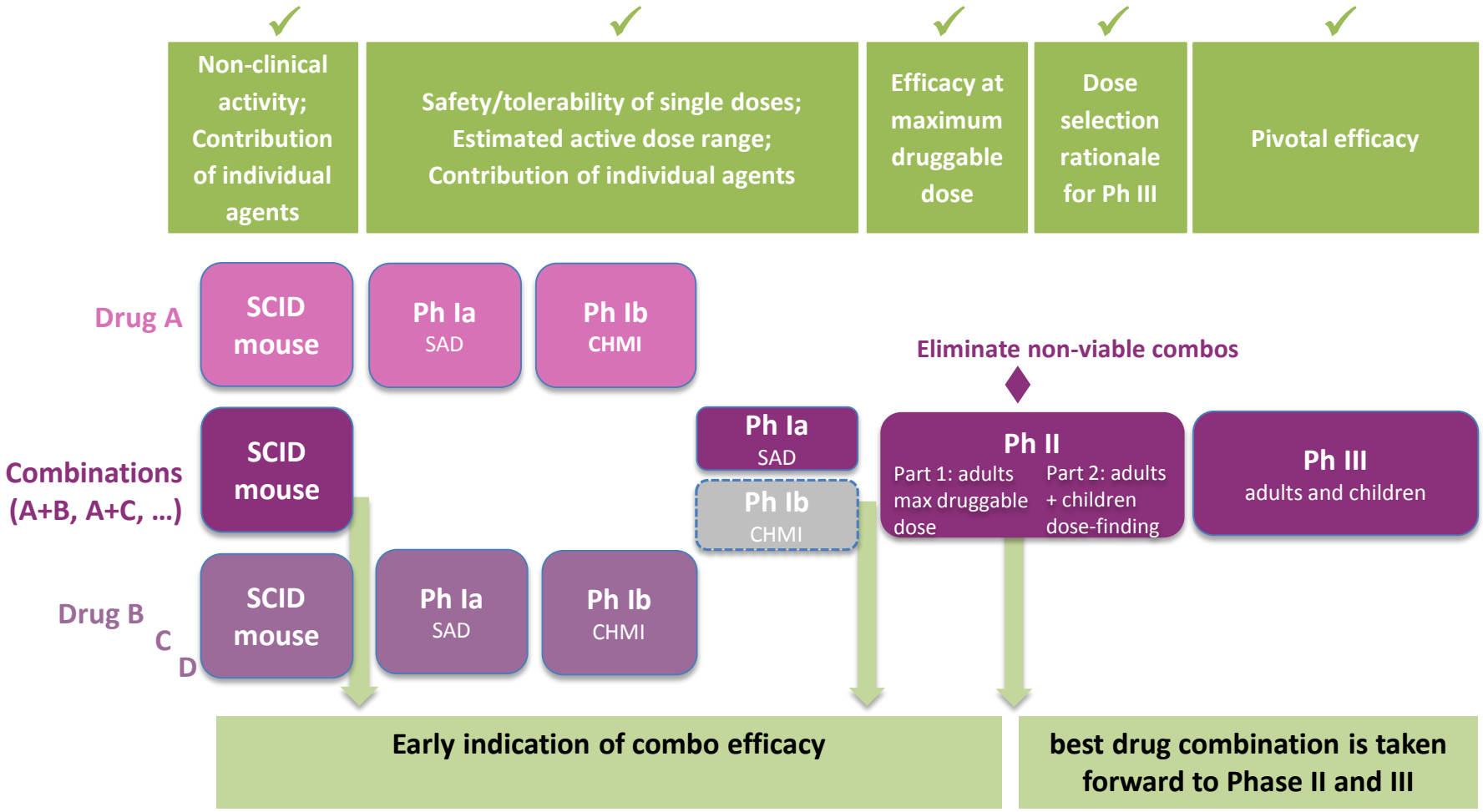


Conclusion

- **The animal experiments and challenge studies, combined with PKPD analysis, can help make decisions on the progression of compounds and priorities within the portfolio**

- **In particular, CHMI studies lend themselves better to collect data to inform the PKPD modeling than patient trials since subtherapeutic doses can be investigated safely**

Perspectives



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MMV Disclaimer

This presentation contains certain forward-looking statements that may be identified by words such as ‘believes’, ‘expects’, ‘anticipates’, ‘projects’, ‘intends’, ‘should’, ‘seeks’, ‘estimates’, ‘future’ or similar expressions, or by discussion of, among other things, vision, strategy, goals, plans, or intentions. It contains hypothetical future product target profiles, development timelines and approval/launch dates, positioning statements, claims and actions for which the relevant data may still have to be established. Stated or implied strategies and action items may be implemented only upon receipt of approvals including, but not limited to, local institutional review board approvals, local regulatory approvals, and following local laws and regulations. Thus, actual results, performances or events may differ from those expressed or implied by such statements.

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Thank you !

- MMV colleagues (Mohammed, Nada, Stephan, …)
- Partners (GSK, TAD, Swiss TPH, QIMR, IntiQuan, etc…)

Backup

Impact of SCID Model on Human Doses Predictions

A reasonable predictive model compared to other disease areas

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

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,e] Iñigo Angulo-Barturen,[f] Santiago Ferrer,[f] María Belén Jiménez-Díaz,[f] María-Santos Martínez,[f] Rob Hooft van Huijsduijnen,[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 (IC_{50}s) were estimated at 2.0 μg/ml and 1.8 μg/ml in the NSG and IBSM models, respectively, aligning with 1.8 μg/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.)

Antimicrob. Agents Chemother. 2016;60:3669-3675

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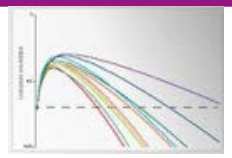
In-vivo models – SCID model help predict human dose and efficacy in pre-clinical stage

In Severe Combined Immuno-Deficiency **(SCID) mouse model,** mouse transfused with **human blood** and **inoculated with *Pf* allows for in vivo testing of compounds for PK, PD, and efficacy modeling**

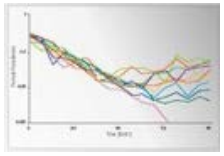
Human blood inoculation to mice → P. Falciparum infection → Administer drug → Data collection & modelling (PK/PD)

Infected human blood

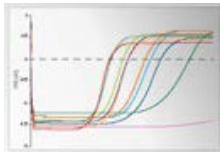
Parasite inoculation (Pf blood stage infection)



Pharmacokinetics (PK): drug concentration vs time



Pharmacodynamics (PD): parasitemia vs time



Modelling: growth/ kill rate vs time in response to drug concentration

Data help predict the human dose and support compound selection

SCID models key insights

- **Estimated in-human efficacy and dosing of individual agents and combination** (in preparation for CHMI studies)
- **Information on how drugs work together** (synergetic, additive, negative) as part of **combination sciences platform** to select additive/synergistic combinations

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Example of integrated impact – PK/PD Modelling of Actelion-451840 allowed an early decision to discontinue before Phase IIa

Translational capabilities use case

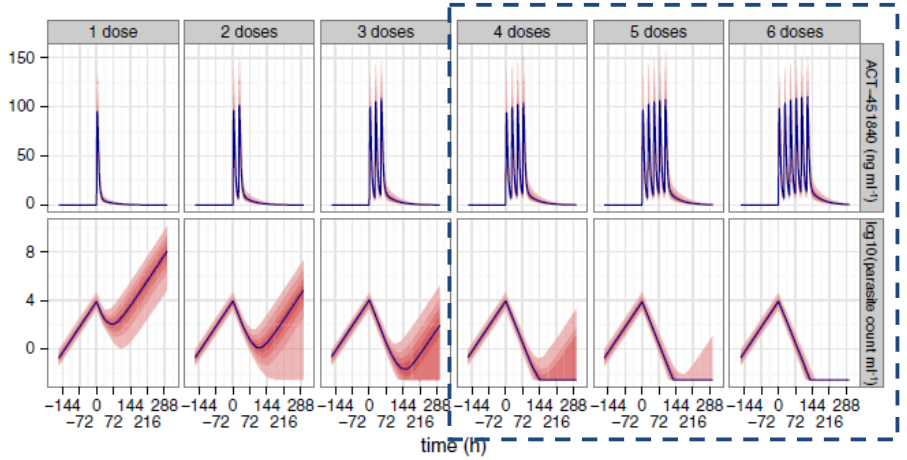
IBSM human challenge model:

- 8 healthy subjects inoculated with 1800 P. falciparum infected red blood cells
- Actelion-451840 500 mg administrated through oral single dose on Day 7
- Parasitemia followed closely to serve as a base to PK/PD modelling
- **PK/PD modelling:** used to estimate parasite growth and the relation to drug exposure, with following simulations to derive estimates of likelihood of achieving cure in different scenarios

Impact

- **7 daily doses** are predicted to be **equivalent to artesunate monotherapy** and **larger doses or more frequent dosing are not predicted to achieve more rapid cure**

Simulated parasite concentration for one to six doses of 500 mg once daily



Dosing allowing to reach sustained parasitemia below 1 parasite/ ml

- As **more than three daily doses** would be needed **to achieve reasonable efficacy,** Actelion-451840 is unsuitable as part of a single exposure cure and has **not been pushed to Phase IIa**
- This allows **to prioritize other most promising candidates** and to save the costs of an expensive Phase II

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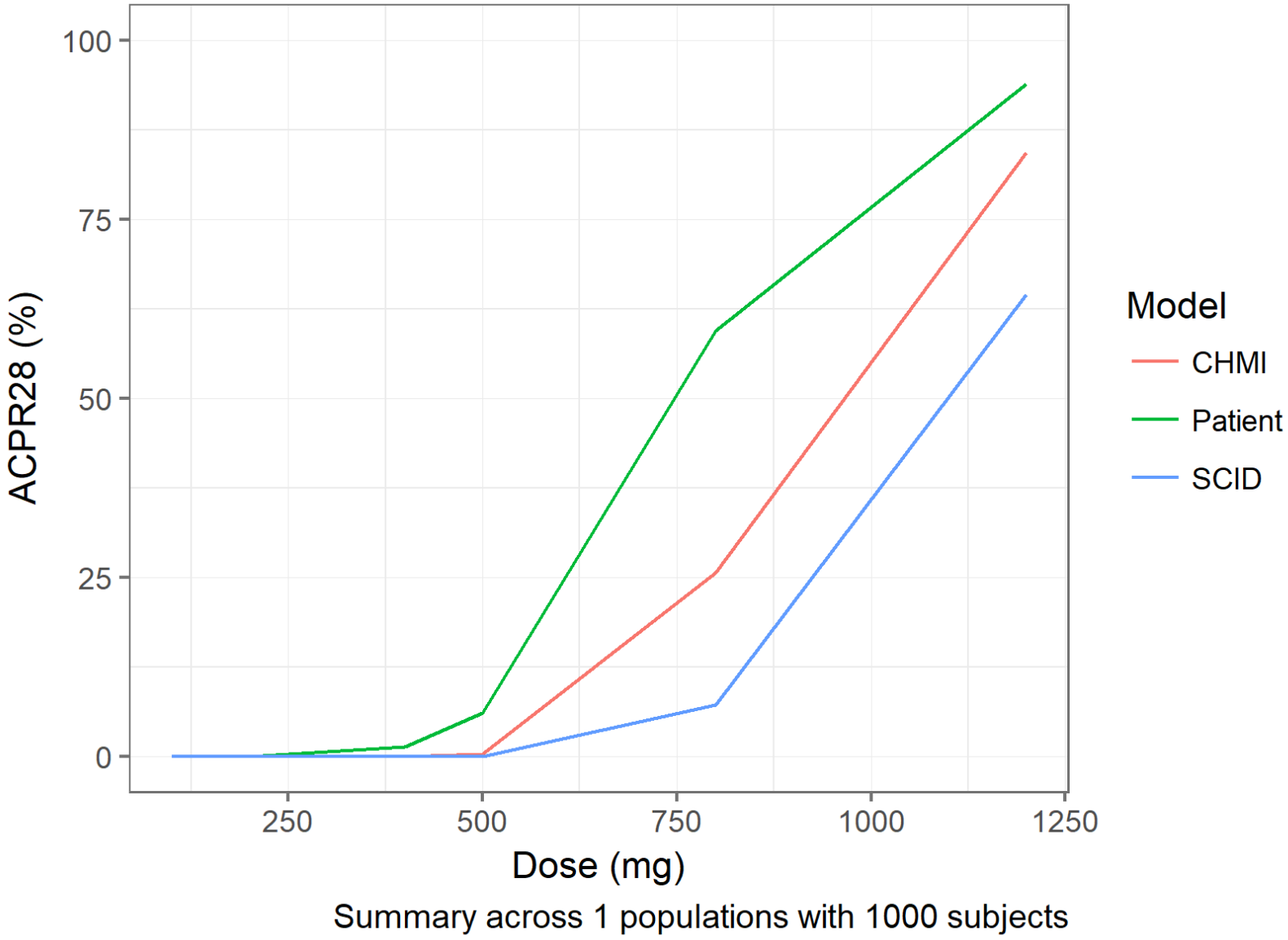
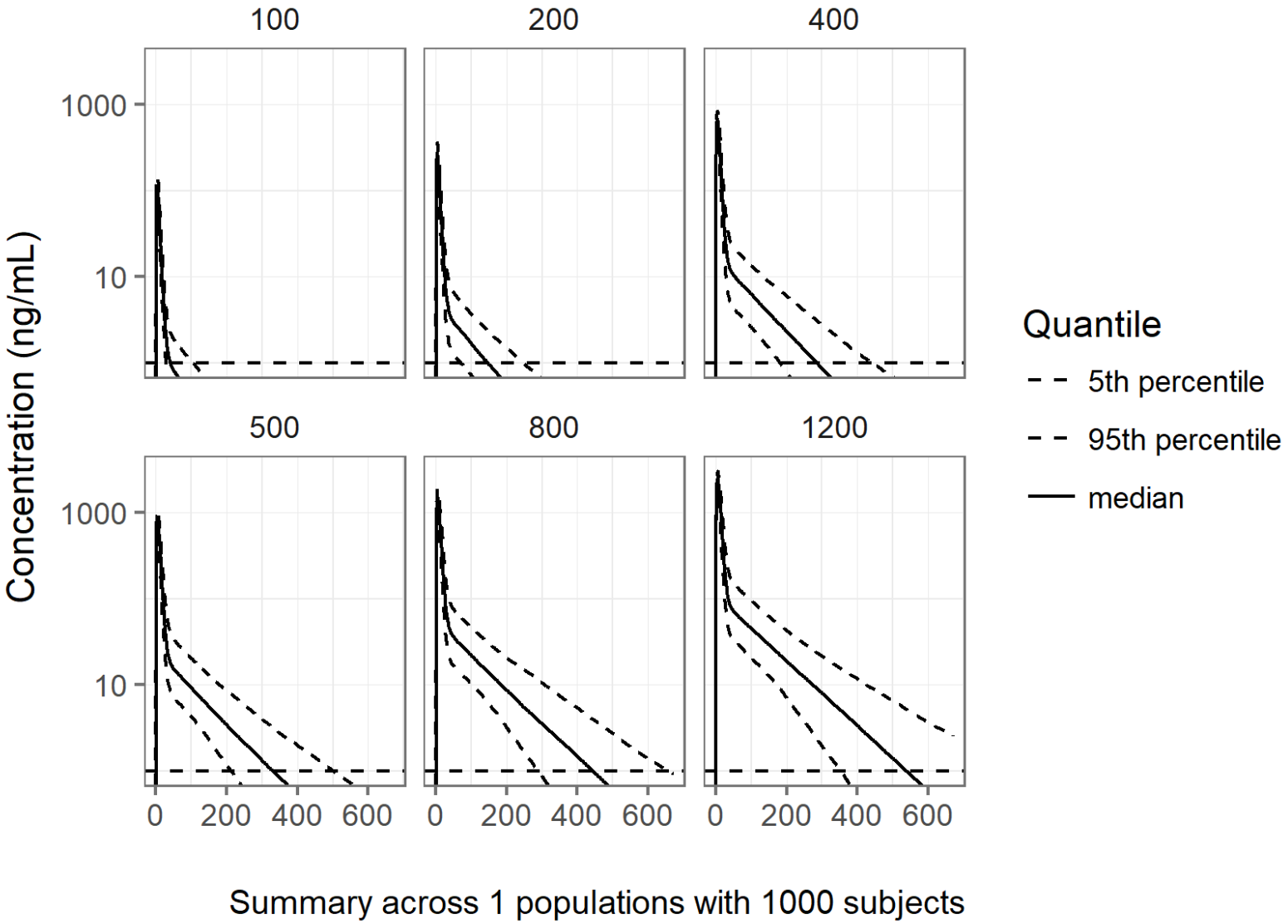
Predicted ACPR28 (Artefenomel)



PK predictions with CHMI data (Artefenomel)



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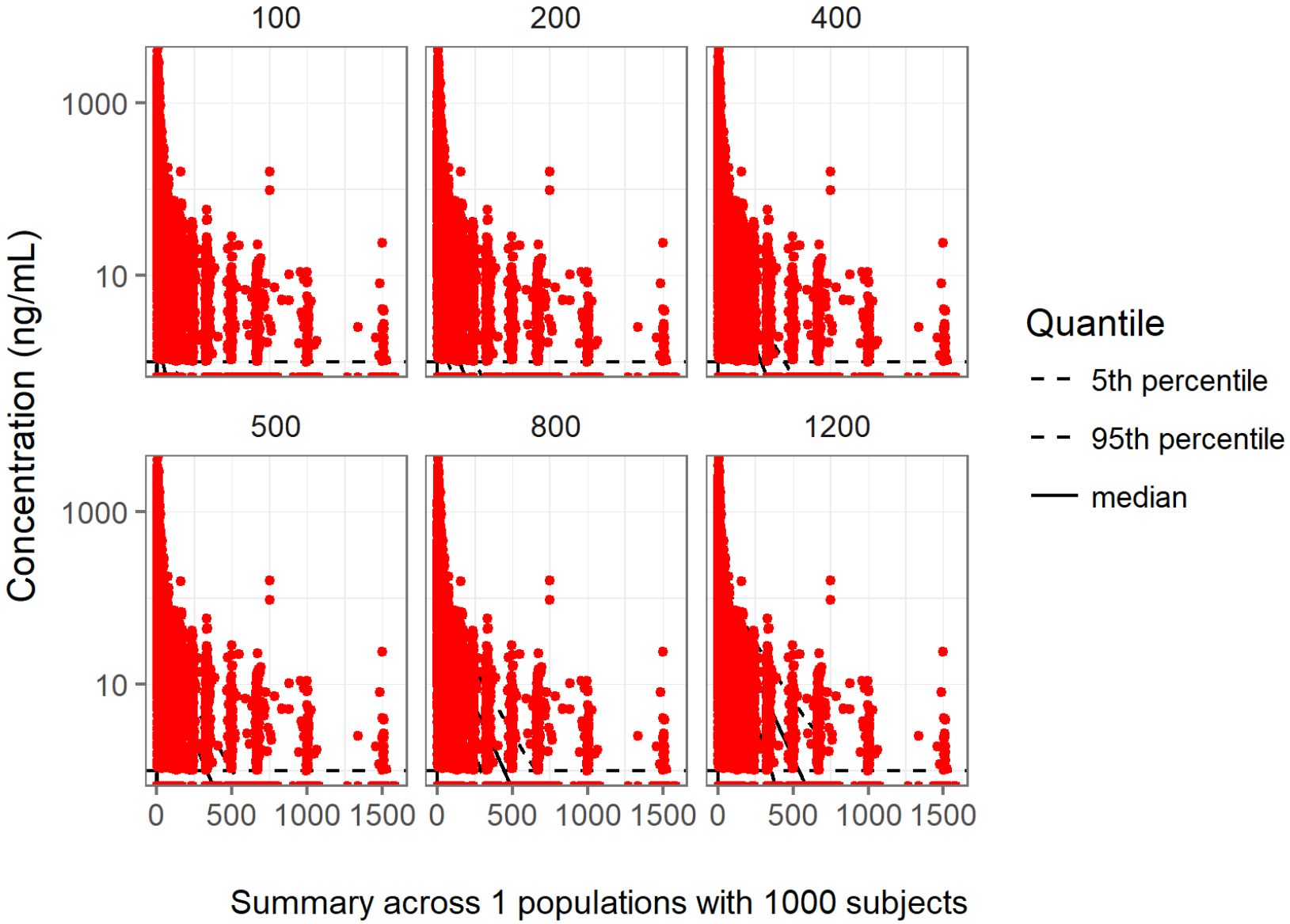
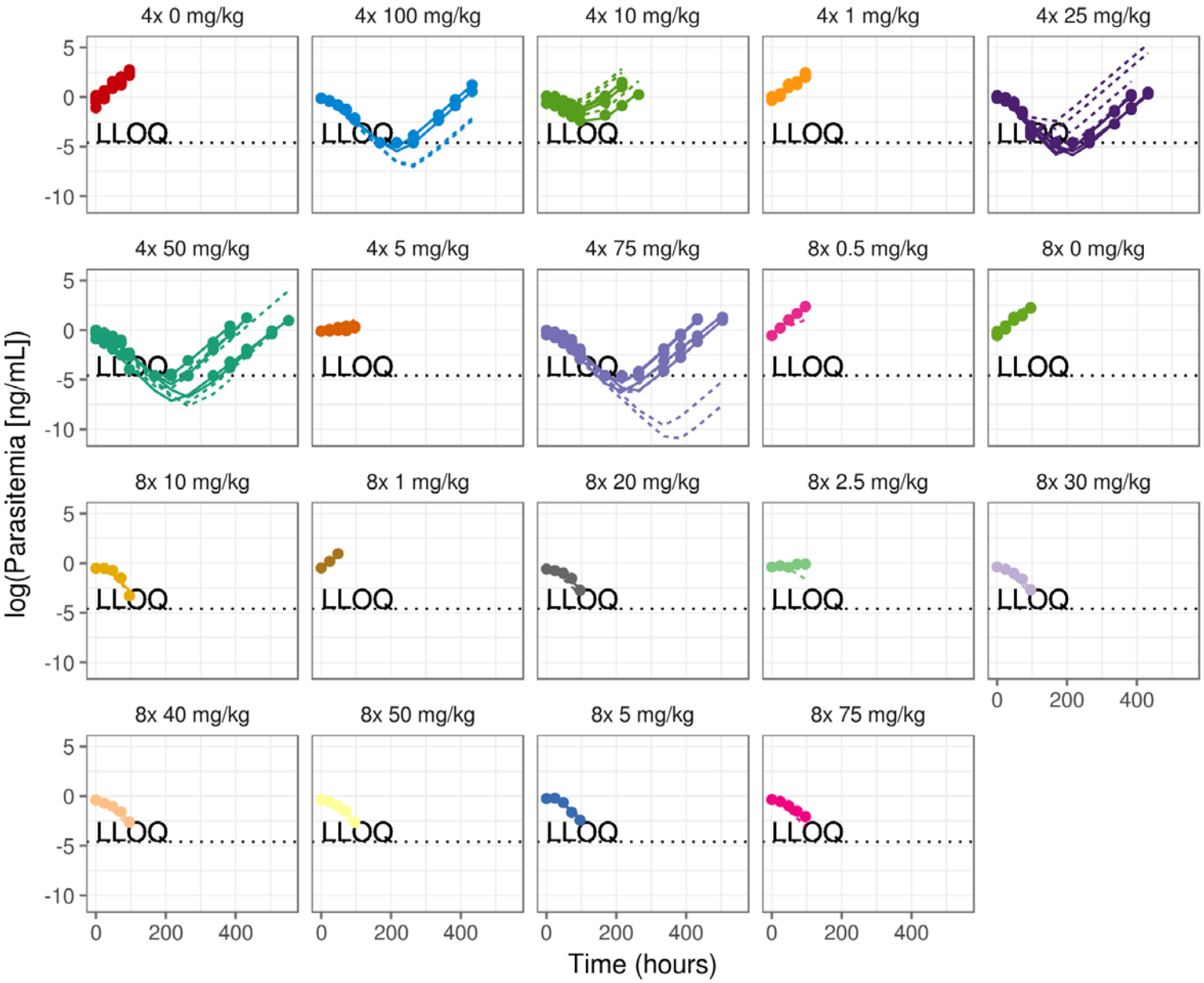
PK predictions with CHMI data (Artefenomel)



Another example: DSM265 (SCID data)



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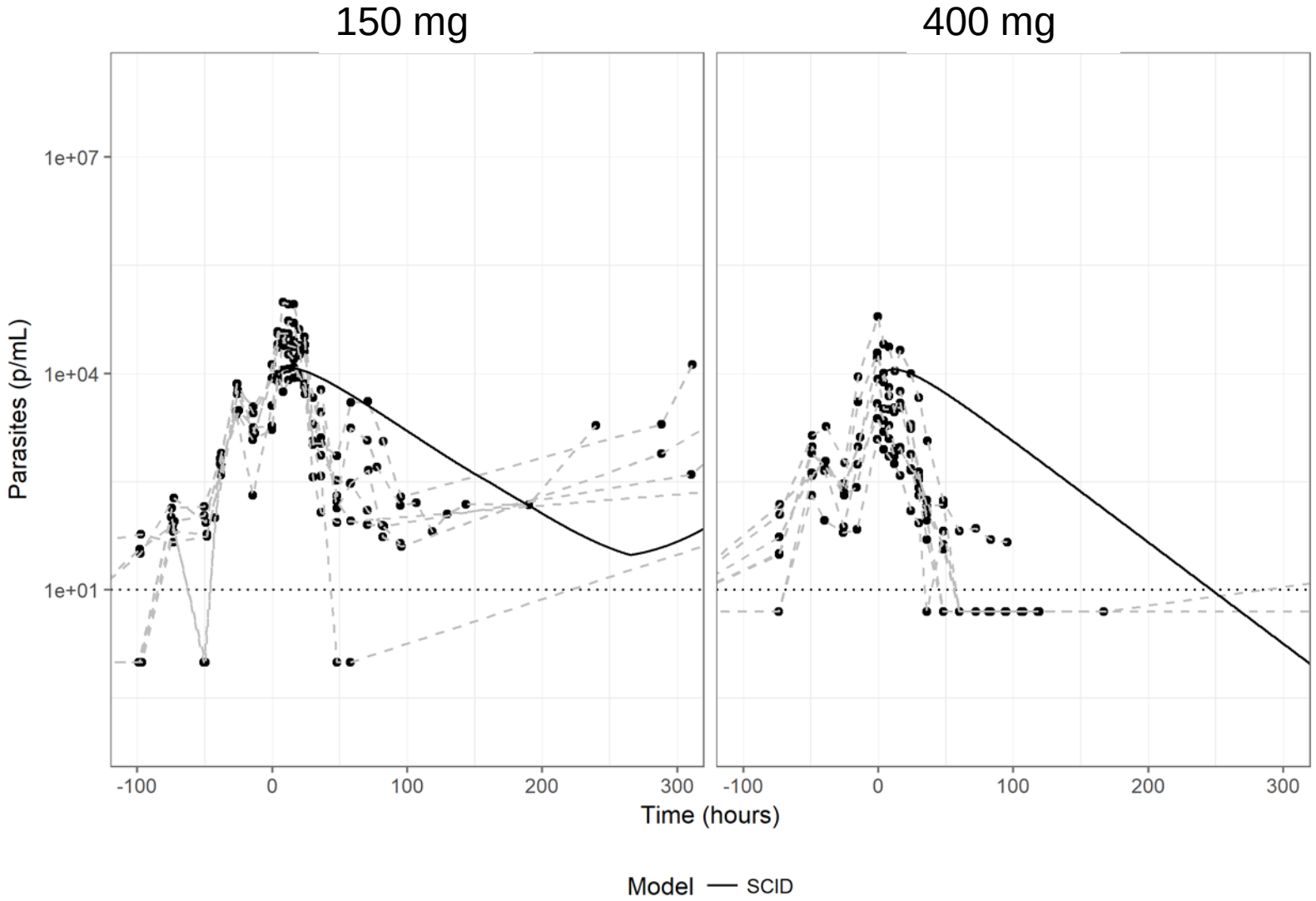
Another example with DSM265
SCID to CHMI



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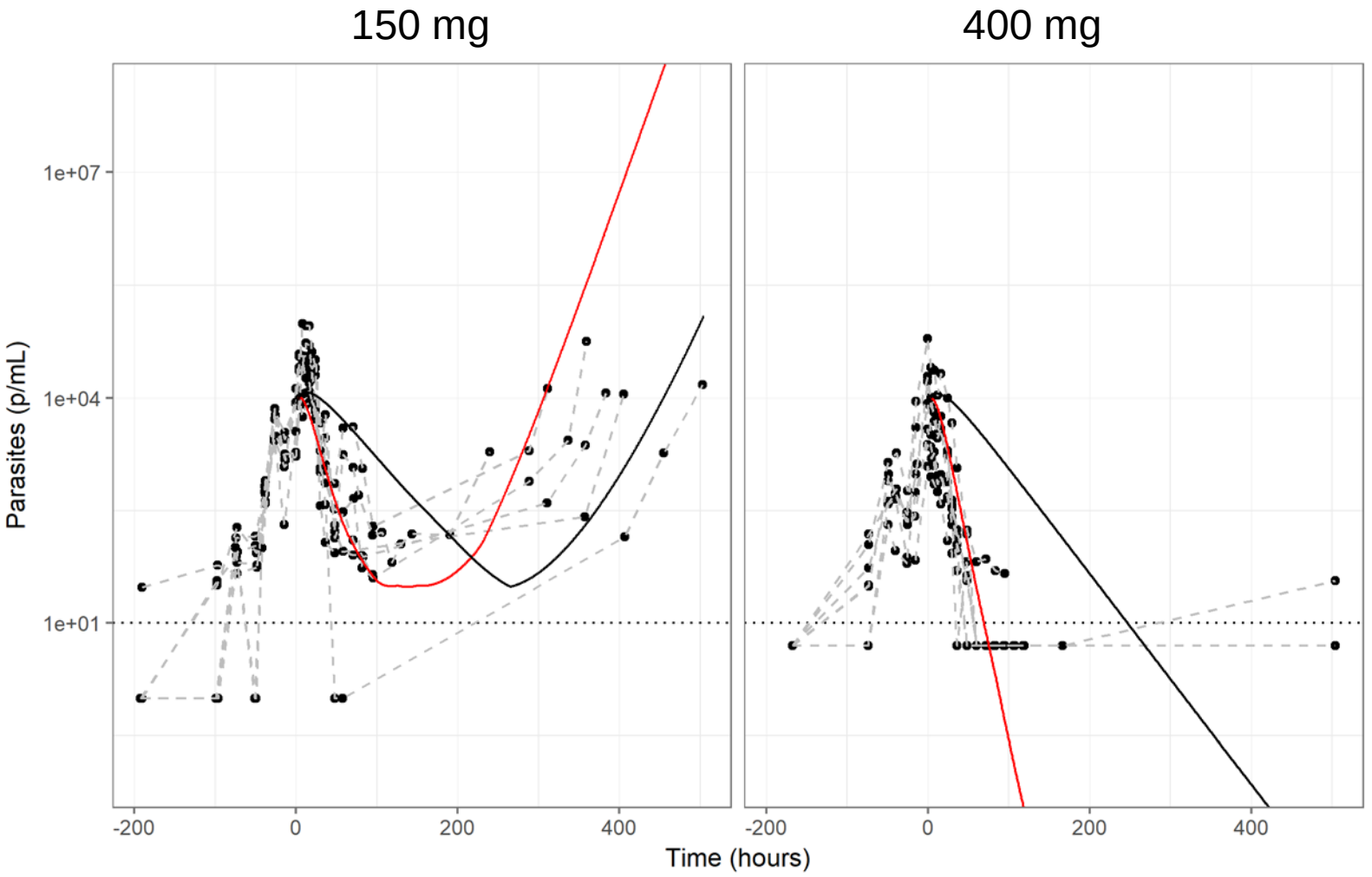
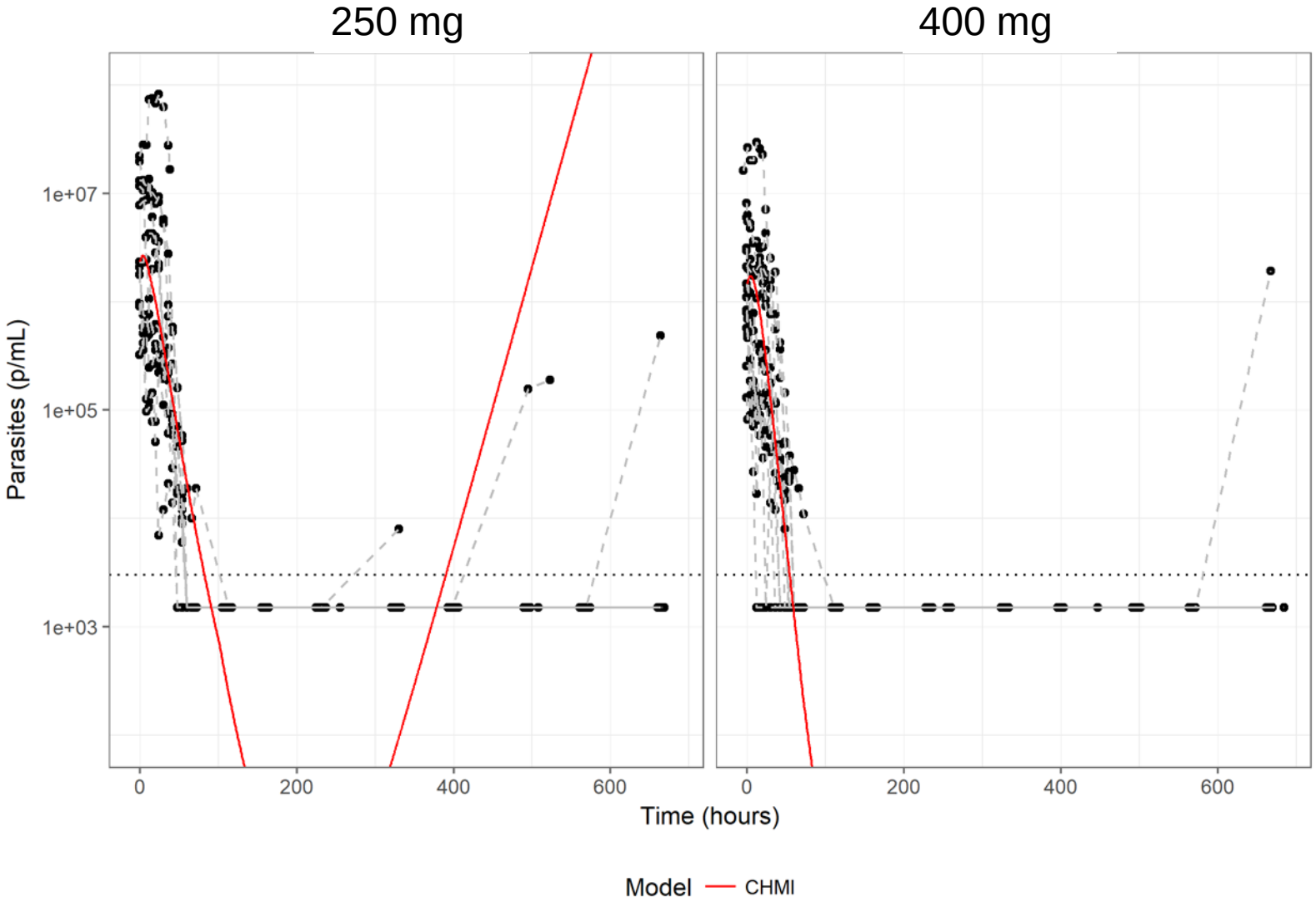
Another example with DSM265
The PKPD model is refined with CHMI data



for Malaria Venture

Another example with DSM265 CHMI to Patients



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Another example with DSM265

- **The PKPD model parameters could not be estimated with patients data only:**

  Too few recrudescences were observed

- **Unlike for Artefenomel, the patients trial was not aimed at identifying the MIC, ie relatively high doses, close to therapeutic doses, were tested**