Pharmacology Considerations for Combination Malaria Treatment

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Medicines for Malaria Venture

What are our challenges?

Case Study OZ439 and DSM265

Contribution for selection of doses

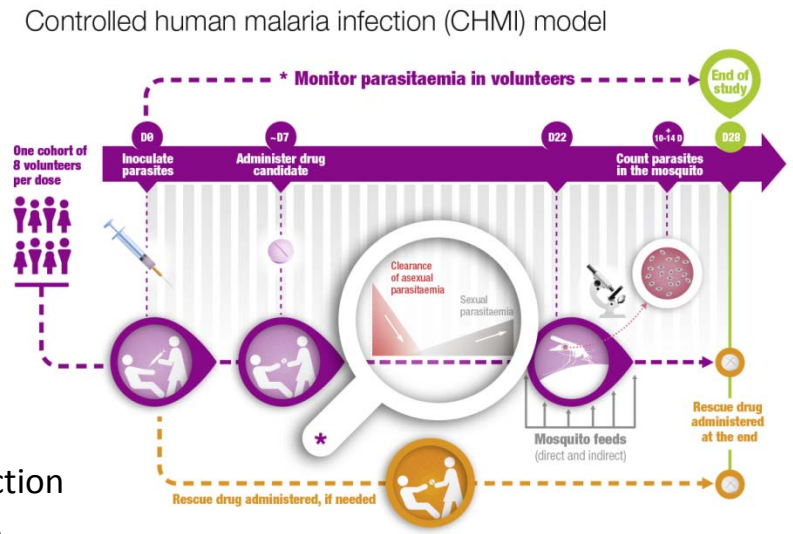
Impact

Challenges

- Combinations required
- How to get the right dose of both compounds
- Operational and ethical obstacles to conduct full factorial design studies
- Large monotherapy study in clinically infected patients are not advisable
- MIC studies are necessary but very difficult to implement in the field
- How to utilise the challenge studies
- Extrapolate to doses in patients with higher baseline parasitemia

Recently published CHMI studies in antimalarial drug development

- McCarthy et al.
  Linking murine and human *Plasmodium* challenge models (AAC (2016) doi:10.1128/AAC.02883-15
- McCarthy et al.
  Efficacy of OZ439 (artefenomel) against early *Plasmodium falciparum* blood-stage malaria infection in healthy volunteers (J Antimicrob Chemother (2016) doi:10.1093/jac/dkw174)
- Pasay et al.
  Piperaquine monotherapy of drug sensitive *P. falciparum* infection results in rapid clearance of parasitemia but is followed by the appearance of gametocytemia (J Infect Dis. (2016) doi: 10.1093/infdis/jiw128)
- Krause et al.
  Pharmacokinetic/pharmacodynamic modelling of the antimalarial effect of Actelion-4 51840 in an induced blood stage malaria study in healthy subjects (Br J Clin Pharmacol (2016))



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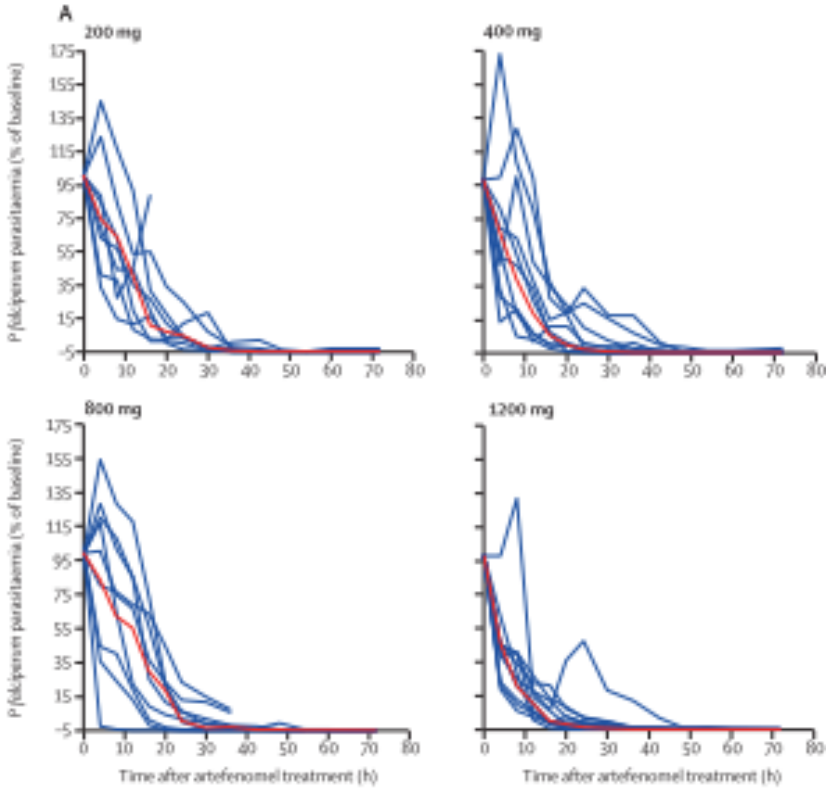
Case Study OZ439 and DSM265

- **OZ439**
  - PoC study in the field
  - Challenge Study
- **DSM265**
  - Phase I and Challenge Study
- **OZ439/DSM265**
  - Combination Challenge Study

OZ439 PoC

- PoC in patients after SAD/MAD/ Food Effect Study
- Phase II a study in patients
- 4 cohorts (200, 400, 800, 1200 mg)
- Standard of care at 36h post OZ439
- Output: PRR, parasite clearance $t_{1/2}$, PCT, FCT

- Oct 2010 – May 2012



Phyo et al. LID, 2015 Volume 16, No. 1,

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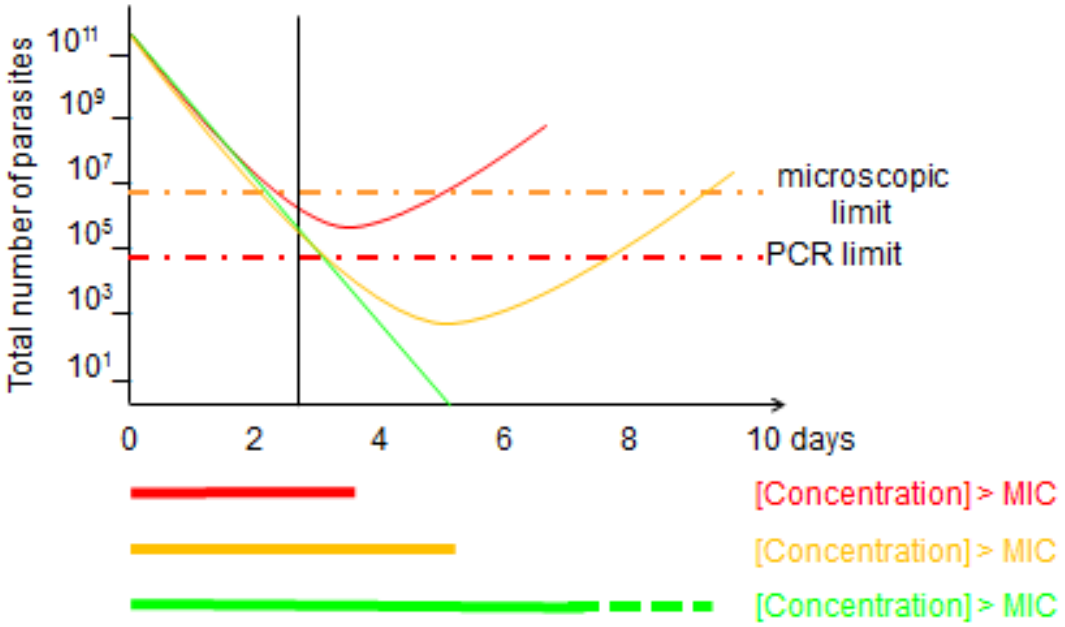
Measuring the MIC clinically



$$P_t = \int_0^t P \,.\, [G - D_0 . (C_t{}^H / (C_t{}^H + IC_{50}{}^H)] . dt$$

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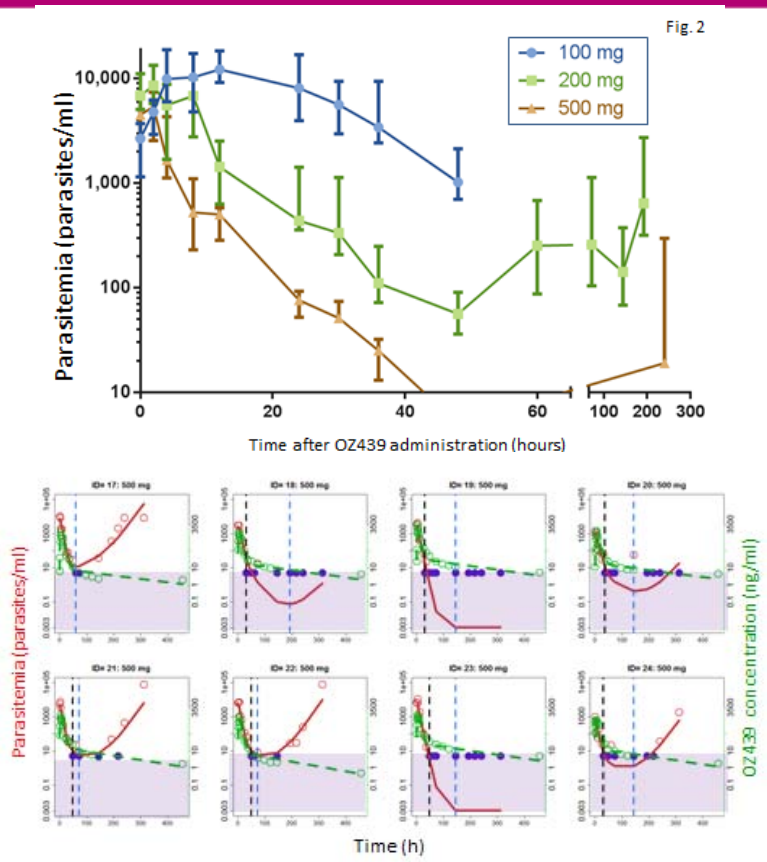
OZ439 Challenge Study

- Single dose 100, 200 and 500 mg
- Follow up to SD16
- At 500 mg,
  - PRR48 >4
  - parasite t1/2 3.6h
  - MIC: 4.1 ng/ml
- Sep 2012 – Feb 2013



McCarthy et al 2016

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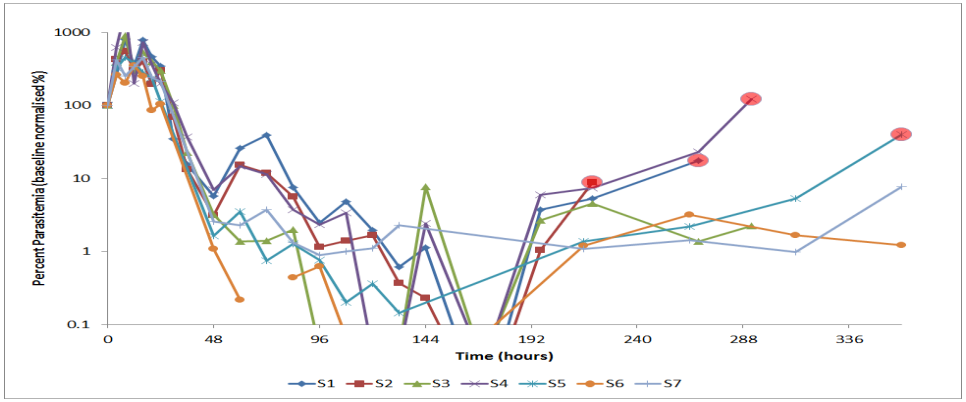
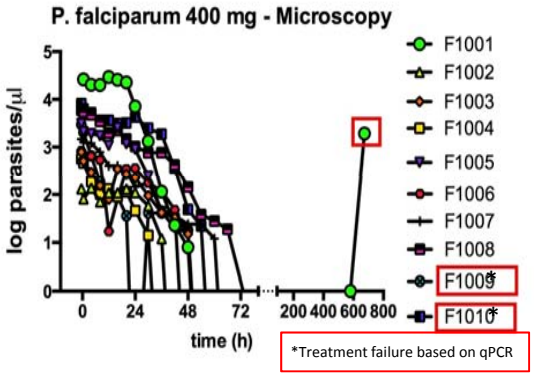
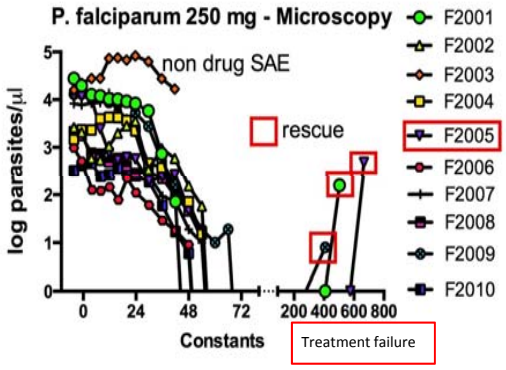
DSM265

- Phase I: SAD & challenge cohort (150 mg)
  - 4/7 recrudescence
  - PRR approx. 2
  - MPC 954 – 1400 ng/ml
  - HED~320 mg
  - 6 month after FiH
- PoC study*
  - *P. falciparum* 2 cohorts (400, 250 mg)
  - Follow up 28 days
  - PRR, lag, MIC,
  - Feb 2015 – Oct 2015







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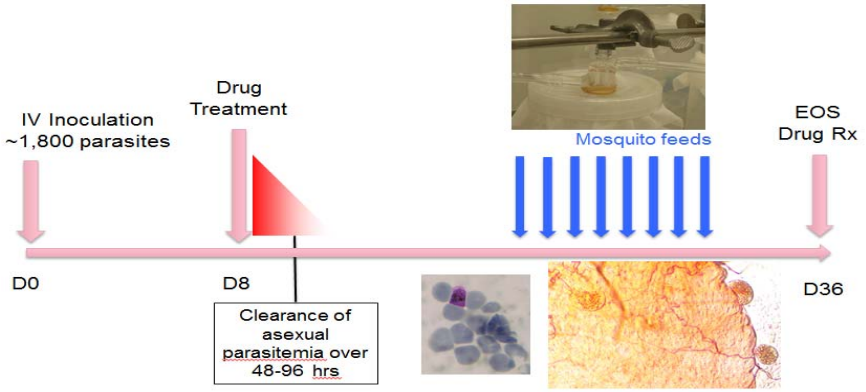
OZ439 – DSM265 combination Challenge study: design

- Selected single dose of each drug which will not eliminate all parasites
  - DSM265: 150 mg 4/7 recrudescence
  - OZ439: 200 mg, 8/8 recrudescence
- Following preliminary modelling work dose:
  - 200 mg OZ439 & 100 mg DSM265: 40% success
  - 200 mg OZ439 & 50 mg DSM265: < 5% success



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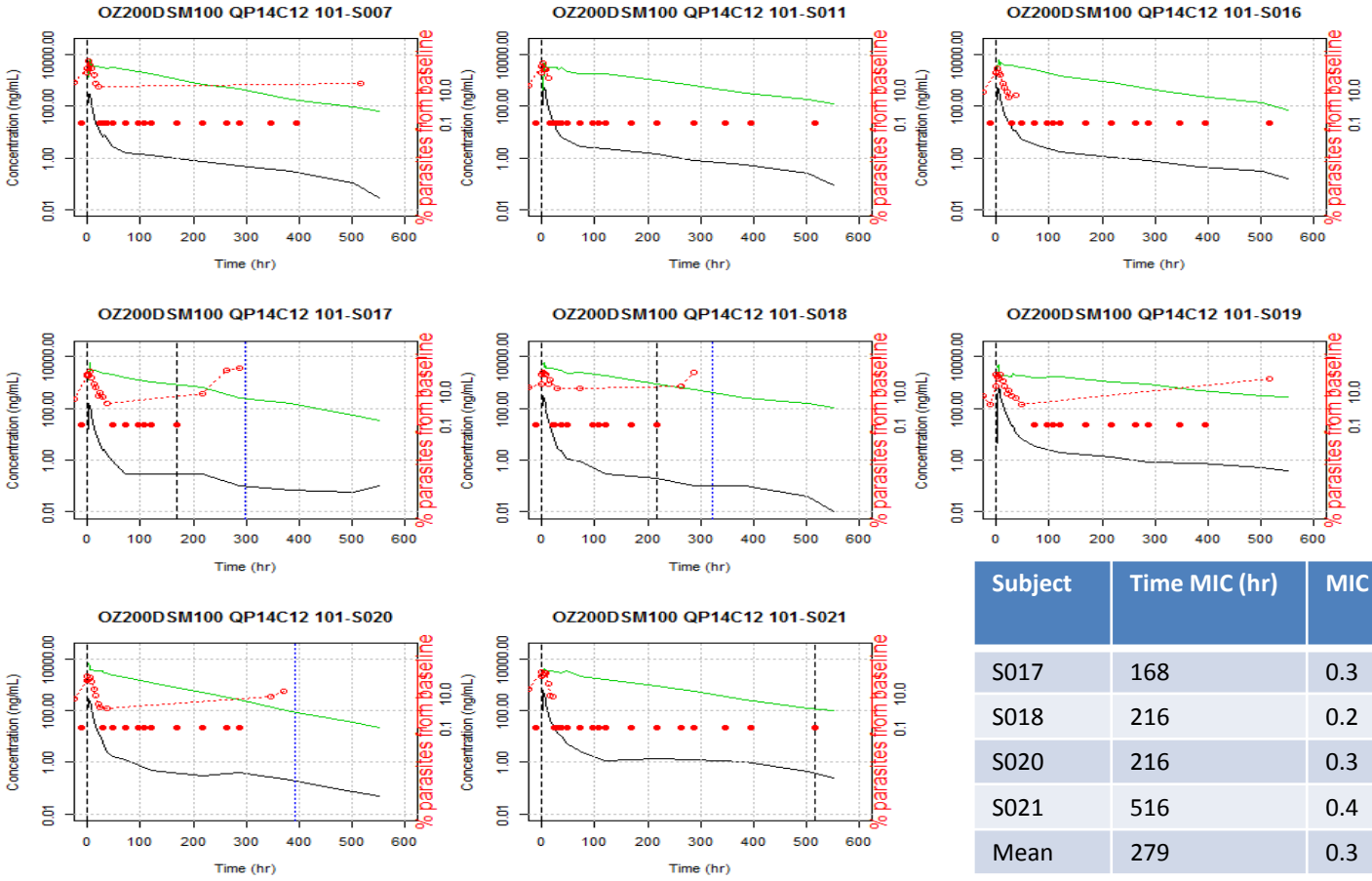
Individual parasitemia profiles: Cohort 200/100



Based on daily qPCR data

OZ439 PK

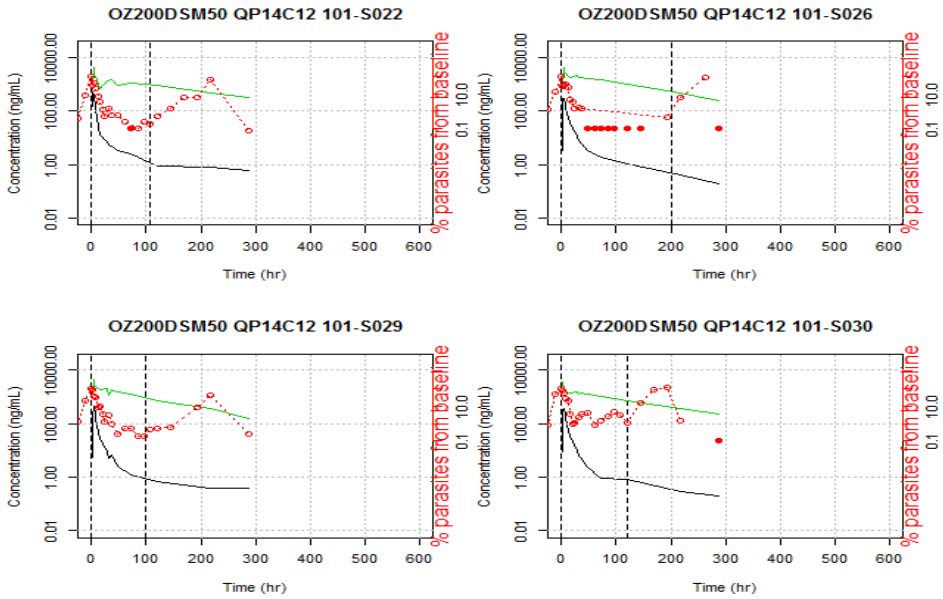
DSM265 PK

Parasites

4/8 subjects recrudesce

Subject	Time MIC (hr)	MIC OZ ng/mL	MIC DSM ng/mL
S017	168	0.3	815
S018	216	0.2	846
S020	216	0.3	521
S021	516	0.4	111
Mean	279	0.3	573

Individual parasitemia profiles: Cohort 200/50



- Below LOQ (=64 /uL)

Based on daily qPCR data

OZ439 PK

DSM265 PK

Parasites

5/5 subjects recrudesce

Subject	Time MIC Hr	MIC OZ ng/mL	MIC DSM ng/mL
S022	108	1.2	987
S026	200	0.5	520
S028	216	2.7	523
S029	100	0.9	896
S030	120	0.8	709
Mean	149	1.2	727

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Parasite killing and MIC

Drug	OZ439 200mg	DSM265 150 mg	OZ/DSM Combo 200 / 100 mg	OZ/DSM Combo 200 / 50 mg
Log_{10} PRR	2.2	1.5	2.8	2.7
95% CI	(2.1–2.3)	(1.4–1.7)	(2.6–3.0)	(2.6–2.8)
OZ439 MIC (ng/ml)	4.1		0.3	1.2
DSM265 MIC (ng/ml)		954–1400	573	709

The model shows the contribution of both drugs on Parasite Reduction Rate and apparent MIC

PD Model

$$\frac{dP}{dt} = P\left(G - D\frac{c^{\gamma}}{c^{\gamma} + IC_{50}{}^{\gamma}}\right)$$

P: parasite concentration
T: time in hour,
G: the first order parasite growth rate in absence of drug
D: the maximum drug-specific parasite reduction rate
C: the drug concentration
IC_{50} the drug concentration required to achieve half the maximum parasite reduction rate
γ: an optional nonlinearity parameter defining the steepness of the concentration-effect curve

INT: The potential PD interaction of the two drugs. If INT is significantly greater than 0 then the two drugs are deemed to be synergetic, and if not, antagonistic.

For OZ439: (E_{max} model)

For DSM265: (E_{max} model)

For Combo:

$$D_{OZ}\frac{C_{OZ}^{\gamma_{OZ}}}{C_{OZ}^{\gamma_{OZ}} + IC_{50_{OZ}}{}^{\gamma_{OZ}}} + D_{DSM}\frac{C_{DSM}^{\gamma_{DSM}}}{C_{DSM}^{\gamma_{DSM}} + IC_{50_{DSM}}{}^{\gamma_{DSM}}}$$

+ INT x E_{max} model for OZ and DSM

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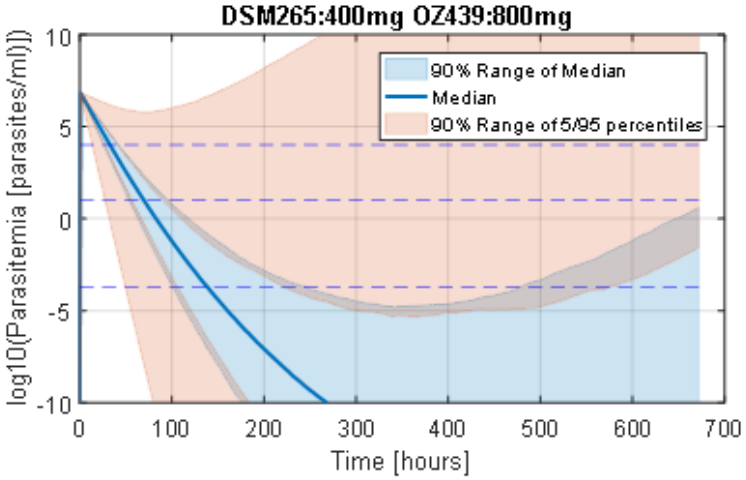
In Preparation: Phase IIa

- Low, non-therapeutic doses are not acceptable
- 2 cohort study in patients
- Two dose combinations will be investigated that predict treatment success based on PK/PD M&S of the CHMI study and higher parasitemia in the field



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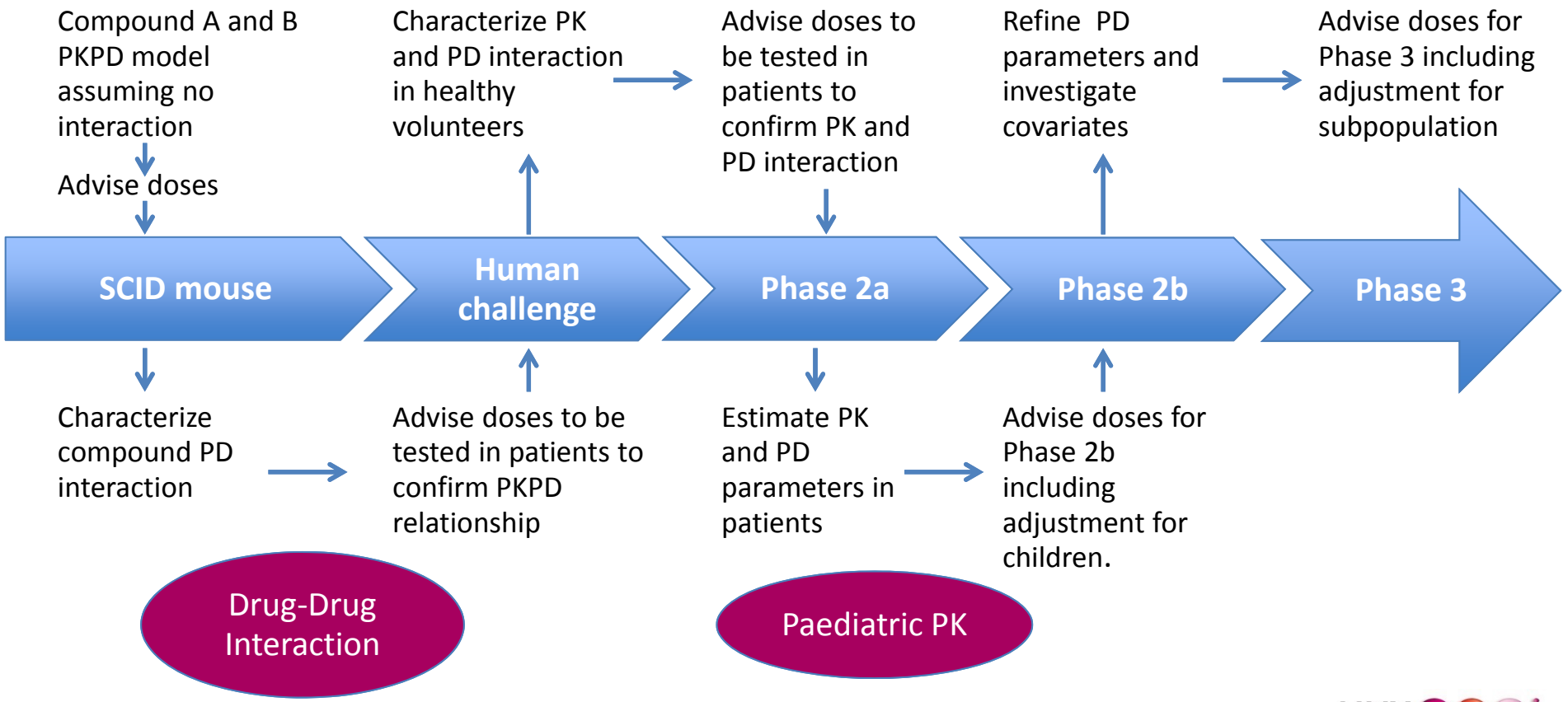
Data generation for PKPD modelling



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Conclusions

CHMI, Modelling and Simulation have been successfully applied

- Generate in phase I PD Information
- Reduce size of first in patient study
- Generate more data (28 f/u)
- Reduce overall time lines
- Show the contribution of each compounds on parasite reduction rate, apparent MIC and probability of success

Acknowledgements

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