

Model-based informed screening of antimalarial combinations

Nathalie Gobeau (1), Mohammed H. Cherkaoui (1), Anne Kümmel (2), Nada Abla (1), Nicole Andenmatten (1), Didier Leroy (1), Jörg Möhrle (1), Francisco Javier Gamo Benito(3), Maria Jose Lafuente-Monasterio (3)

(1) MMV, Geneva, Switzerland, (2) IntiQuan GmbH, Basel, Switzerland (3) GSK, Tres Cantos, Spain

Background

Malaria is treated with combination therapies in order to minimize resistance. However, resistance is unavoidable and therefore the hunt for new treatments must continue. The ambitious objective of MMV is to develop new single-dose combinations that are as efficacious as the current three daily doses. Hence combinations must be identified so that two compounds together lead to a higher cure rate than each one individually. There are now 8 antimalarial new molecules in the MMV portfolio which have already shown promising efficacy as monotherapy in humans – either in Volunteer Infection Studies (VIS) or patient trials. From the large number of potential combinations of these candidates, the most promising ones need to be determined and progressed into late stage development.

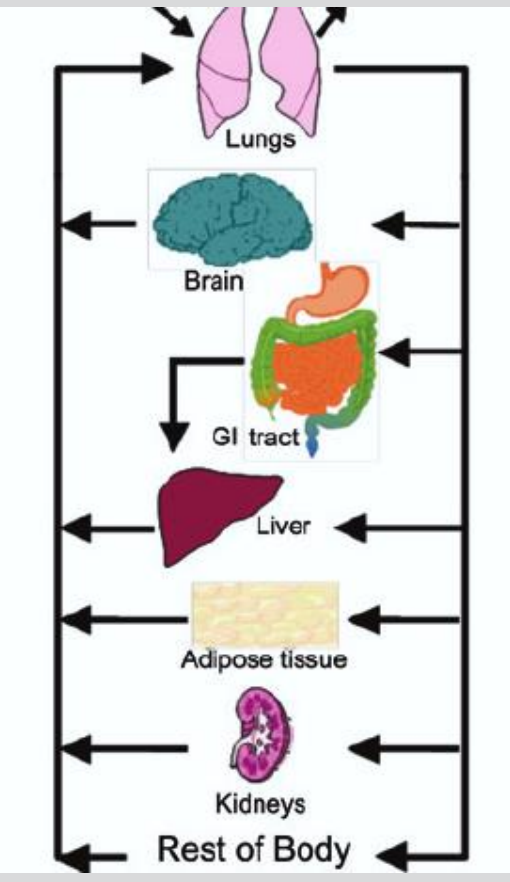
Objectives

MMV aims to develop a strategy to screen a large number of combinations and select the most promising ones, i.e. the most likely to achieve the same efficacy with a single dose as the current treatments which require three daily doses.

Methods

PK interaction

- PBPK model:**
- a PBPK model is built with the First-In-Human studies of each compound administered as monotherapy
 - Interaction between the compounds is assessed *in vitro*
 - If the *in vitro* assessment indicates a possible PK interaction, the PK of each compound in the presence of the other is predicted by PBPK.



PD interaction

General pharmacodynamic model [1]

Parasite counts (log-transformed):
$$\frac{dPL}{dt} = \left(GR - \frac{E_{max,21} \cdot C_1^{H1}}{C_1^{H1} + EC_{50,21}^{H1}} - \frac{E_{max,12} \cdot C_2^{H2}}{C_2^{H2} + EC_{50,12}^{H2}} \right)$$

Interaction on max. clearance:
$$E_{max,ij} = E_{max,j} \left(1 + (e^{\beta_{ij}} - 1) \frac{C_i^{Hi}}{C_i^{Hi} + EC_{50,i}^{Hi}} \right)$$

Interaction on potency:
$$EC_{50,ij} = EC_{50,j} \left(1 + (e^{-\alpha_{ij}} - 1) \frac{C_i^{Hi}}{C_i^{Hi} + EC_{50,i}^{Hi}} \right)$$

An experiment in severe combined immunodeficient (SCID) mice engrafted with human erythrocytes and infected by *P. falciparum* is undertaken to test the combination and used to identify the parameters.

Human PKPD projection

- A PKPD model is built with data in challenge volunteers or patients for each compound as monotherapy.
- The general pharmacodynamic model is used to make predictions of the parasitemia profiles in patients with
 - $E_{max,i}$, $EC_{50,i}$, $Hill_i$ parameters: same as monotherapy data in challenged volunteers or patients
 - Interaction parameters (α_{ij} , β_{ij}): same as SCID mice experiments
 - Compound concentration: from the PBPK model
- The cure rate at day 28 (ACPR28) is calculated.

Results

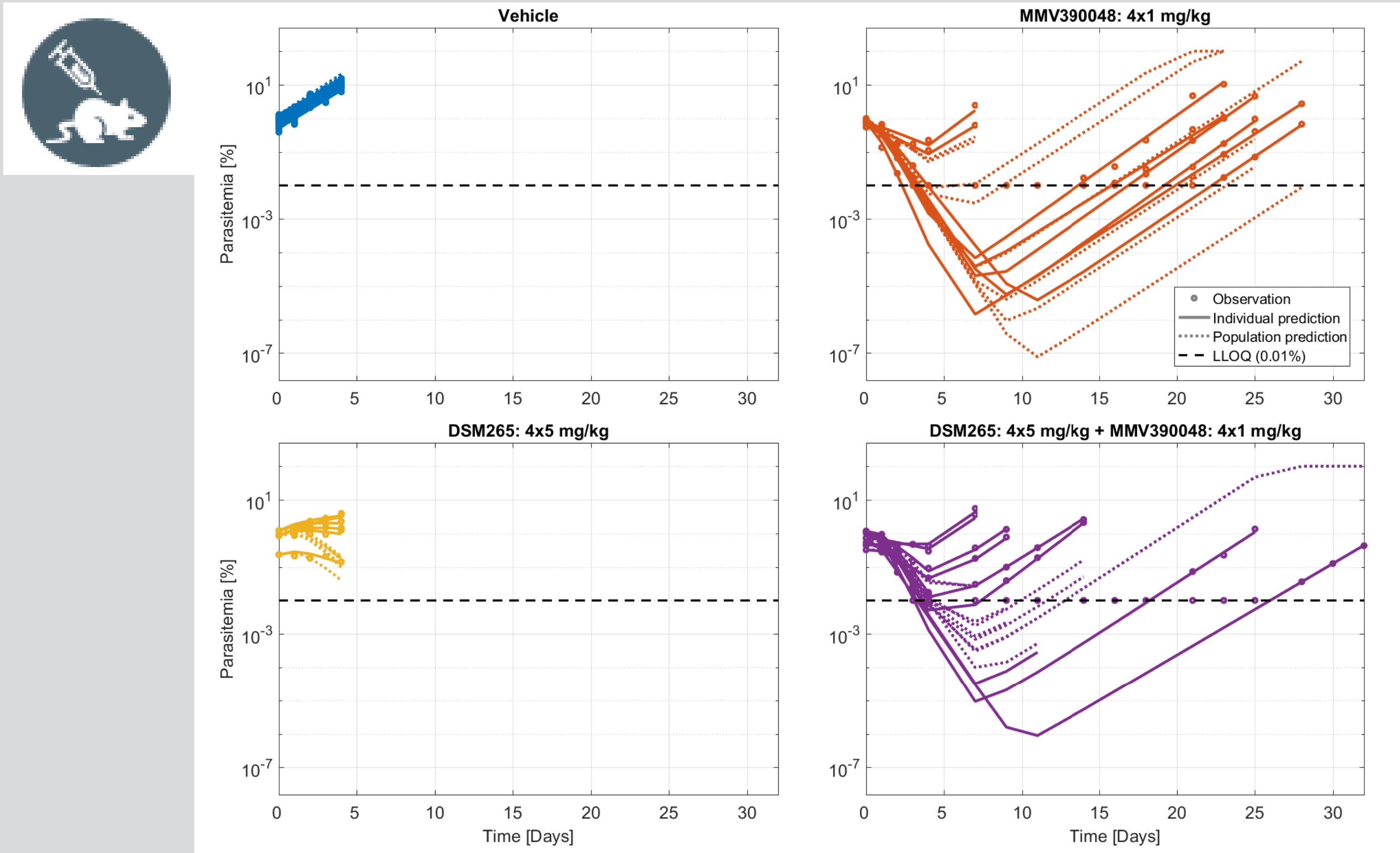
Identification of PD interaction parameters

- A SCID mouse experiment was undertaken in which several combination doses of DSM265 and MMV048 were tested (see table). Each compound was tested as monotherapy at the doses used in the combo. In addition, monotherapy data over a wider dose range from previous experiments was added to the dataset.

DSM265 (4 Doses)	MMV048 (4 Doses)				
	In mg/kg	0.25	0.5	1	2.5
	5		X	X	
	10	X	X	X	
	25		X	X	X

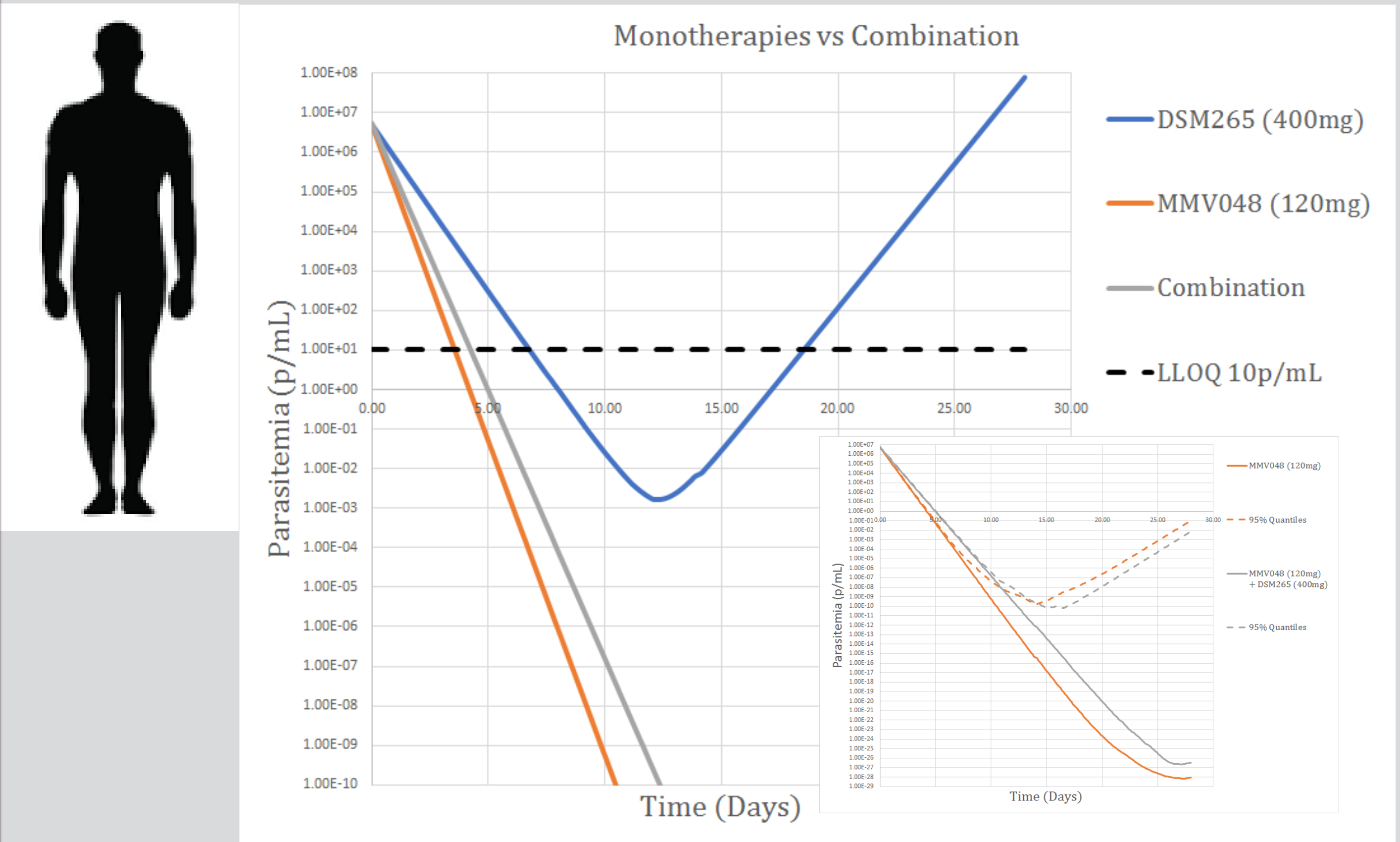
- PK concentrations and daily parasite counts were measured in each mouse over one month;
- The selection of the best model was based on:
 - Lowest sum of squared difference of predicted and observed time to recrudescence
 - Best BIC
 - Simplest model

- The PD interaction parameters for DSM265 and MMV048 were found to be $\alpha_{12} = \alpha_{21} = \beta_{21} = 0$; $\beta_{12} = -1.55$



Human projection

- Both DSM265 and MMV048 were tested as monotherapy in a VIS in which PK and PD were measured in each subject. From these studies, a PKPD model was built for each compound as a monotherapy
- The *in vitro* DDI assessment suggested a potential interaction since the major metabolite of DSM265 inhibits the enzyme UGT1A1 which metabolizes MMV048. However simulations in Simcyp showed the interaction was not significant. Hence the PK interaction was ignored.
- The two monotherapy challenge PD models were combined with the equations above assuming the interaction parameters were the same as in mice
- From the predicted parasitemia profile, the ACPR28 was calculated: the ACPR28 of the combo was only marginally better than the ACPR28 of the best compound.



Conclusions

12 combinations will be tested this year in the mouse model. It is expected that the current strategy will be able to identify at least the combinations which will lead to an ACPR28 higher than the ACPR28 of each individual agent, and at best allow to rank the different combinations according to their predicted ACPR28 or total number of parasites killed. This will allow to prioritize the combinations that progress into the VIS study to confirm the predictions before going into patients.

References

[1] Wicha et al, Nature Communications (2018) 8, 2129

