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Population pharmacokinetics of KAF156/LUM-SDF and exposure-response analysis for the probability of cure for patients with uncomplicated malaria

Giulia Lestini,[1] Ivan Demin,[1] Jing Yu [2]

[1]Novartis Pharma AG, Basel, Switzerland; [2]Novartis Pharmaceuticals, Cambridge, Massachusetts, USA

Background

Novartis in collaboration with Medicines for Malaria Venture (MMV) is developing the novel antimalarial ganaplacide (KAF156, class of imidazolopiperazines) in combination with a reformulated version of the approved antimalarial lumefantrine (a solid dispersion formulation, LUM-SDF, which has an improved bioavailability) for the treatment of uncomplicated malaria due to *P. falciparum* with or without infections with other *Plasmodium* species. This is in line with World Health Organization (WHO) guidelines, recommending the use of fixed-dose combinations of two anti-malarial drugs, to reduce or prevent the risk of resistance development.

KAF156/LUM-SDF combination has previously been studied in a phase 2 dose and regimen finding study (NCT03167242, see Figure 2) that demonstrated that KAF156/LUM-SDF once daily for three days is effective and well-tolerated in patients 2 years of age and older under fasted condition.

Objective

- To describe the population pharmacokinetics (popPK) of KAF156 (KAF) and LUM-SDF when given in combination to fasted adult/adolescent and pediatric malaria patients (≥ 2 years)
- To describe exposure-response (ER) relationship for probability of cure based on PCR corrected (PCR-cor.) ACPR29 (Adequate Clinical and Parasitological Response measured at day 29)
- To evaluate the effect of different covariates on PK and on probability of ACPR29
- To predict PK of both KAF and lumefantrine as well as possible trial outcomes for ACPR29 for candidate phase 3 dosing regimens according to the planned phase 3 design

### Figure 1: Phase 2 (NCT03167242) study design
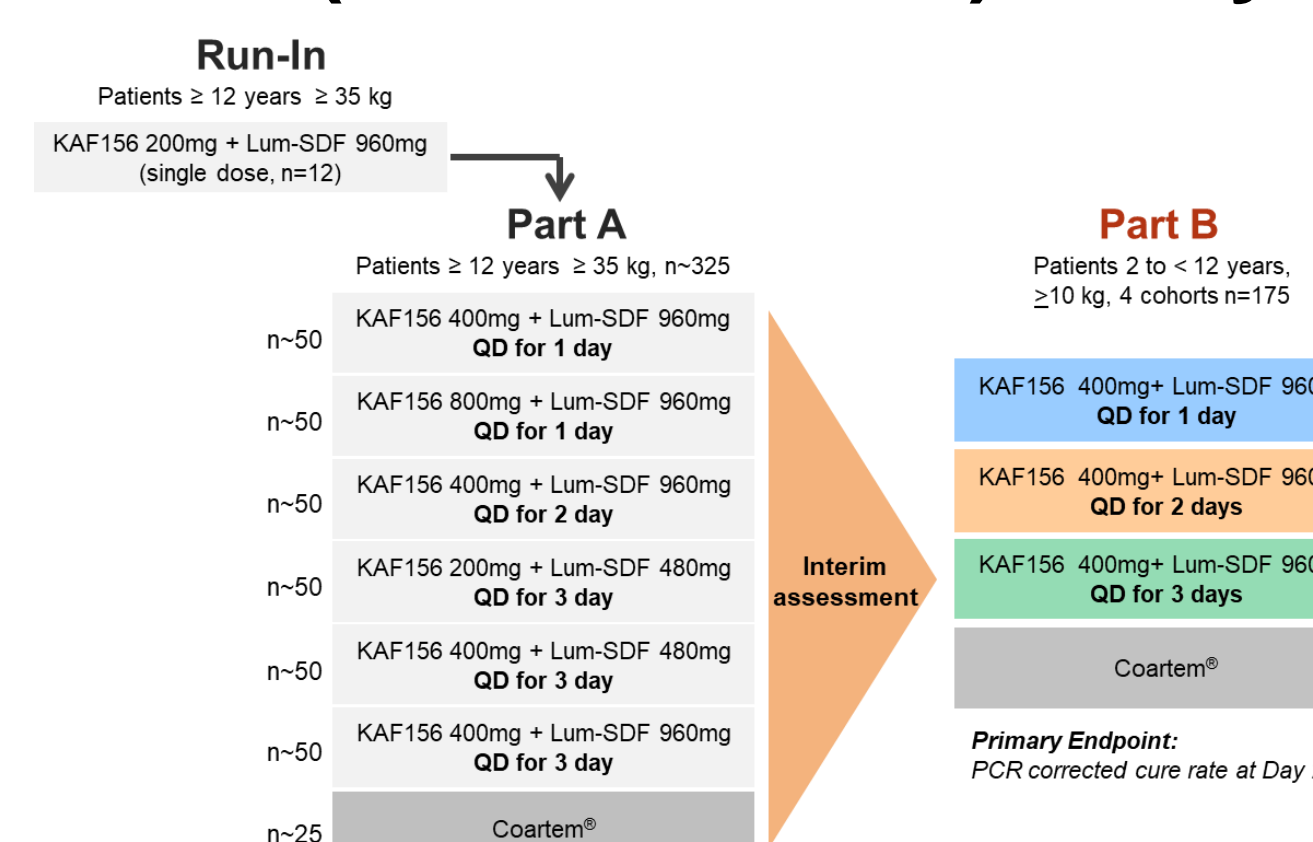
The dose for children was adapted according to patient's body weight: 25.0 to <35.0 kg patients took 75% of adult dose; 15.0 to <25.0 kg patients took 50% of the adult dose and 10.0 to <15.0 kg patients took 0.25 of the adult dose.

Method

The modeling and simulation workflow is presented in Figure 2.

Individual probabilities of cure from ER simulations were used to simulate individual outcomes for each patient (cure or failure) and then were summarized by trial replicate to calculate an outcome (the rate of ACPR29) of each simulated trial. The simulated trial outcomes were summarized and the mean together with 5th and 95th percentiles of the responder rate were calculated for each simulated dosing regimen (see Table 2 and Table 3).

Figure 2: Schematic representation of data flow, modeling and simulation
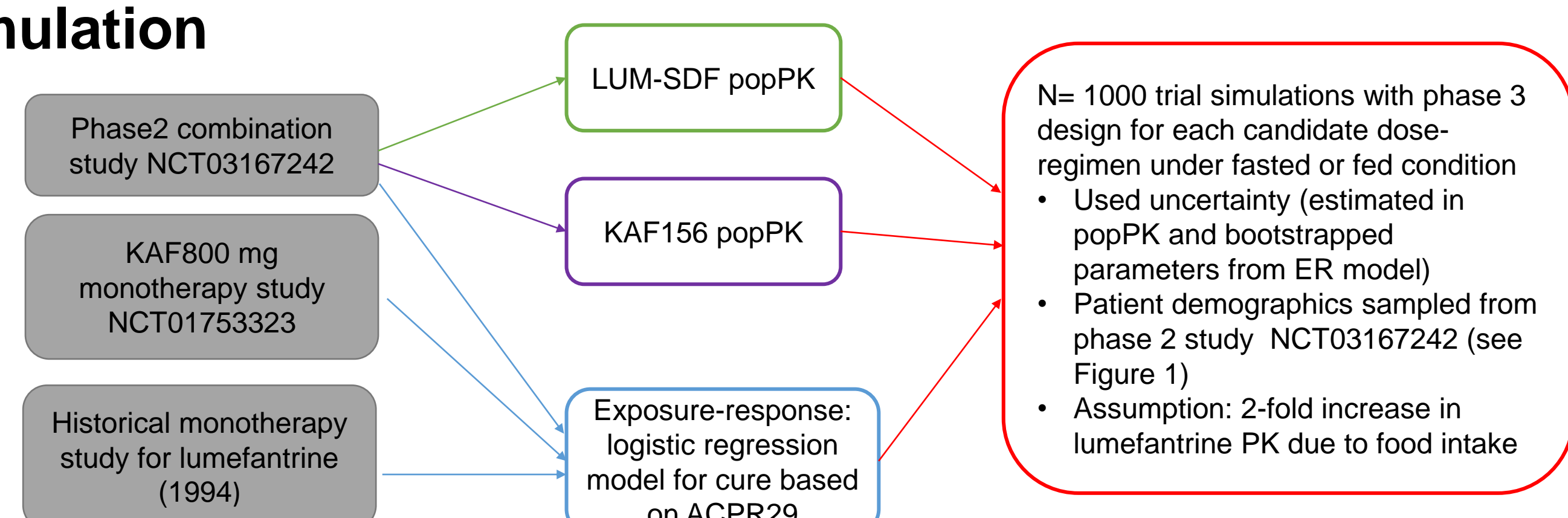
Results

- Final KAF and LUM-SDF popPK models: two-compartment model with first-order absorption, lag time to absorption and first-order elimination. In addition, a relative bioavailability (F) was used in LUM-SDF popPK model
- For LUM-SDF, observed dose non-proportionality of PK between 960 mg and lower doses as well as higher than expected exposure after day 1 were modeled as covariates on F
- PopPK covariates: body weight, indicating increasing apparent clearances and volumes with increasing body weight
- ER data are displayed in Figure 3; final ER model parameters are shown in Table 1. ER model visual predictive check (VPC) is presented in Figure 4

Figure 3: Scatter plot of model-based KAF156 and LUM-SDF Cday7 in Study NCT03167242, colored by cure status and part
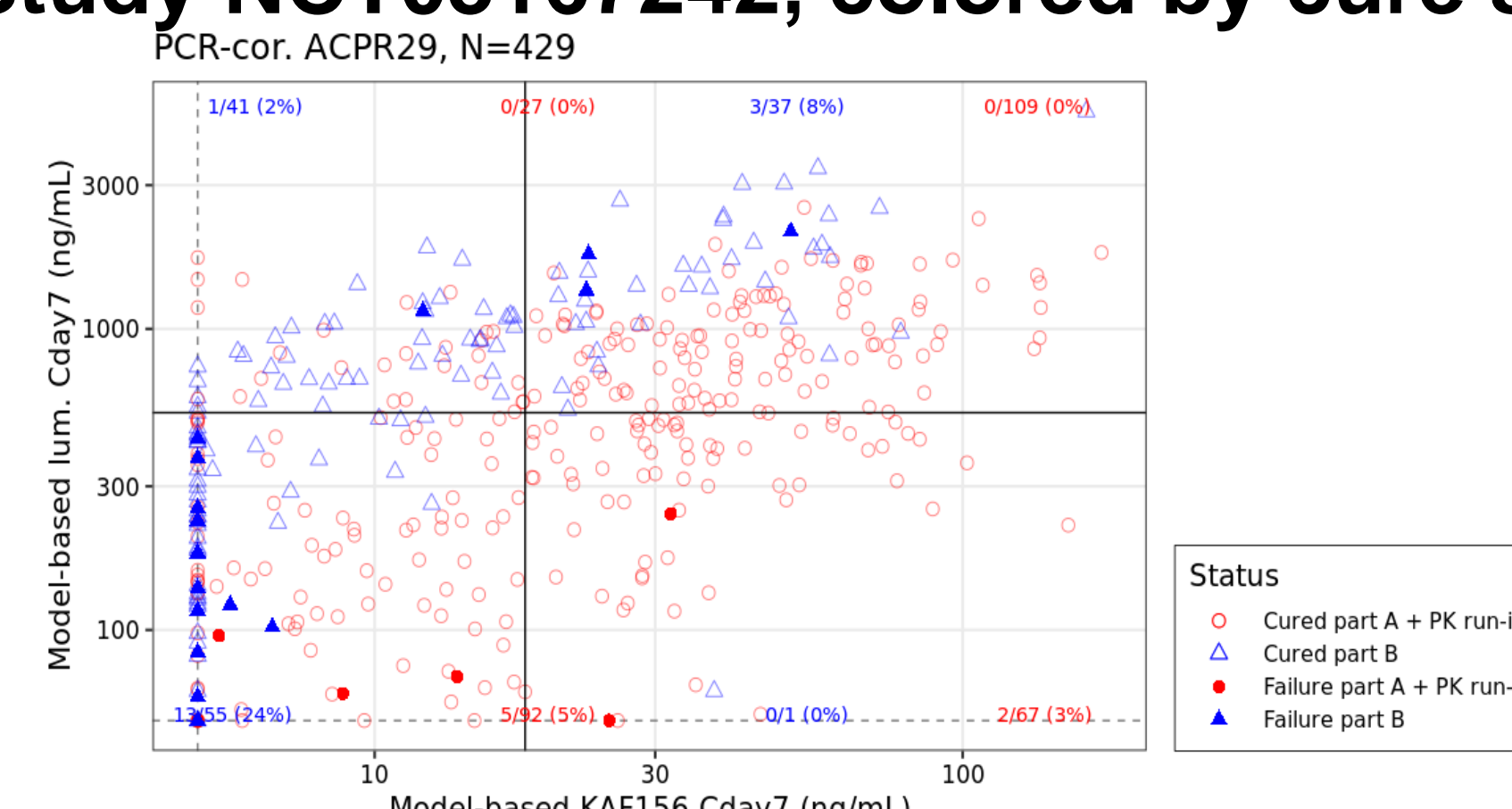

Cday7: concentrations at day7; Black vertical and horizontal lines are the overall medians of KAF156 and lumefantrine Cday7, respectively; n/N (%): show number of non-responders (n), total number of patients (N) and percent non-responders (p) for each quadrant and part;

Table 1: Final logistic regression model parameter estimates with KAF and lumefantrine Cday7 as exposure metric

Parameter name	Estimate	Std. Error	Pr(>|z|)
Intercept	-1.146	1.827	0.530
Baseline parasitemia	-0.088	0.172	0.611
KAF Cday7	**0.346**	0.152	**0.023**
Lumefantrine Cday7	**0.863**	0.140	**<0.001**
Age: adolescents	-0.010	0.601	0.987
Age: children	**-1.684**	0.549	**0.002**

First column: estimated parameter values (through maximum likelihood) for each coefficient based on available data. The second column displays the standard error associated with each estimate. Third column reports the two-sided p-value (Pr(>\|z\|)) showing which coefficients are statistically significant (in bold), i.e., statistically different from 0;
Reference category for age effect is adults (18 years old and older); "Age: adolescents": age effect in adolescents 12-17 years old; "Age: children": age effect in children 2-11 years old

Figure 4: Visual predictive check for the final exposure-response model, by treatment arm and age category
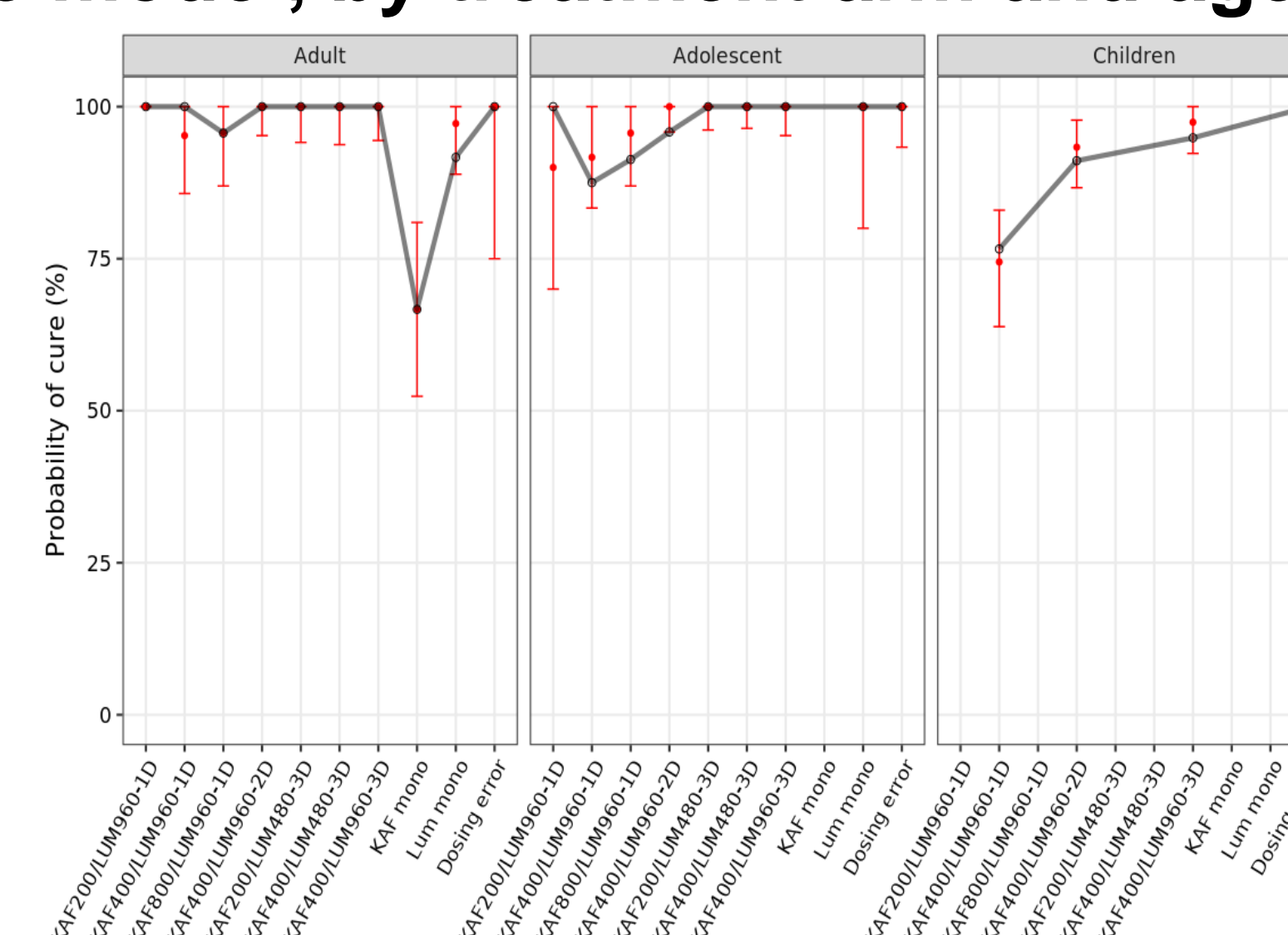
Red: model simulation with 90% uncertainty; black: observed data (point estimates);

Table 2: Predicted responder rates for candidate phase 3 dosing regimens

Dosing regimen	Food	Responder rate for ACPR29 (%)
KAF400/LUM480-3D	Fasted	96 [92 - 98]
KAF400/LUM480-3D	**Fed**	**98 [95 - 99]**
KAF400/LUM480-3D	Fed on D2, D3*	97 [95 - 99]
KAF400/LUM480-3D	Fed on D3**	97 [94 - 99]
KAF400/LUM960-3D	*Fasted*	*97 [95 - 99]*

Design considerations: ~637 patients per arm, 60% being children <12 years, lowest body weight is 5kg;
Mean [5% and 95% percentiles] of predicted responder rates across N=1000 simulated trial outcomes are shown;
*Fed on D2, D3: fasted on Day 1 and fed on Day 2 and 3;
**Fed on D3: fasted on Day 1 and 2 and fed on Day 3;
Italic: target dosing regimen; bold dosing regimens that matches best the exposure of the target

Table 3: Predicted responder rates for candidate phase 3 dosing regimens in children 2 to <12 years old

Dosing regimen	Food	Responder rate for ACPR29 (%)
KAF400/LUM480-3D	Fasted	93 [88 - 97]
KAF400/LUM480-3D	**Fed**	**96 [92 - 99]**
KAF400/LUM480-3D	Fed on D2, D3*	96 [92 - 99]
KAF400/LUM480-3D	Fed on D3*	95 [90 - 98]
KAF400/LUM960-3D	*Fasted*	*96 [92 - 99]*

Design considerations: ~384 patients per arm, children <12 years, lowest body weight is 5kg;

Conclusions

- PopPK and ER models were used to simulate PK and efficacy of untested dosing regimens to further strengthen the evidence base for KAF/LUM phase 3 dose selection

- Based on ER analysis both KAF and lumefantrine exposures contributed to the probability of cure. When assuming 2-fold increase of lumefantrine exposure due to food intake, KAF156 400 mg and LUM-SDF 480 mg once daily for 3 days in fed patients matched efficacy of the target dosing regimen KAF156 400 mg and LUM-SDF 960 mg once daily for 3 days in fasted patients, which showed adequate efficacy in phase 2 study.

Acknowledgment