EMA EFPIA workshop
Break-out session no. 3

Case Study Title: Evaluation of fixed dose combinations in paediatric indications - Use of pharmacokinetic bridging across ethnic groups

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Background & Rationale

- The fixed-dose combination of atovaquone and proguanil was used to **illustrate the consequences of covariate interactions, as determined for the effects of body weight and ethnicity on the pharmacokinetics of both compounds**.

A population pharmacokinetic model was developed for each compound using plasma concentration data from adult patients in an initial population (Africans). PK parameter estimates were then sed to simulate drug exposure in African children using allometric and Bayesian methods. Subsequently, the model was used to predict drug exposure in Oriental children following different dose levels taking into account the effects of body weight.

Without evidence of ethnic differences in drug disposition from clinical trials in Orientals, modelling of the effect of body weight alone does not suffice to provide accurate dosing recommendations in the Asian population. Furthermore, we show that in order to achieve comparable target exposure across both populations, different dose ratios may be required across age groups.

Scaling across populations

TARGET: Dose rationale for a fixed-dose combination should ensure comparable exposure across populations.

APPROACH: *Data from PK in a reference adult population was analysed using a model-based approach.*

Model parameter estimates were subsequently used to predict exposure in a new (ethnically diverse) population using allometric scaling and Bayesian priors.

M&S Assumptions

The main assumptions/requirements included:

1) The anti-malarial effect and mechanism of action of the two compounds is the same in adults and children, as well as across different ethnicities.

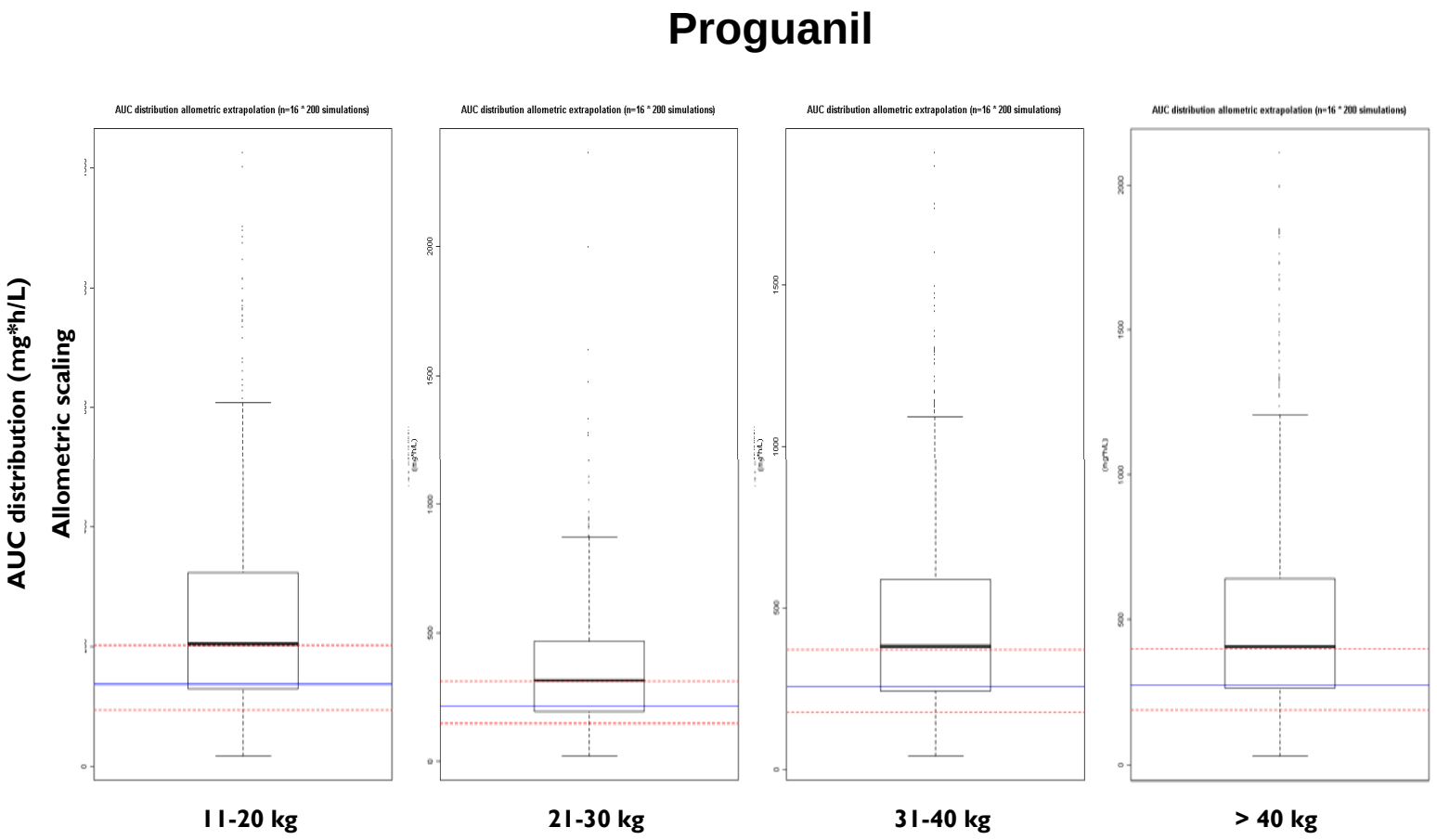
2) Fixed ratio between doses is warranted if the influence of size on drug exposure can be described by a linear function.

3) The effect of size is the main cause of differences across groups.

4) Simulations were performed to demonstrate the implementation of pharmacokinetic bridging and estimate the required dosing requirements

5) Given the wide therapeutic window, fixed-dose combinations were to be considered even if systemic exposures showed deviations from the proposed target range, but ensured levels above a predefined threshold.

Predicted AUC distribution in Orientals



M&S Results

Pharmacokinetic analysis (adult data)

Separate models were developed for ATV and PGN using the adult data only. A one-compartment model with first-order absorption and elimination best described the pharmacokinetics of each compound. The effect of BW on volume of distribution (V) was characterised by a linear correlation. For PGN ethnicity was found to be the only covariate affecting both CL and V. Inter-individual variability was estimated for all fixed effects parameters, i.e. CL, V and absorption constant (Ka). All diagnostic measures (diagnostic plots, NPDE and bootstrap, data not shown) indicated acceptable goodness-of-fit and model performance. The area under the curve (AUC0-∞) was then calculated and used as target exposure for the purposes of bridging. Mean estimates were 368.7 mg*h/L for ATV and at 13.6 mg*h/L for PGN.

Ethnicity (Africans or Orientals) was found to be a covariate on the clearance (CL) of ATV.

M&S Results

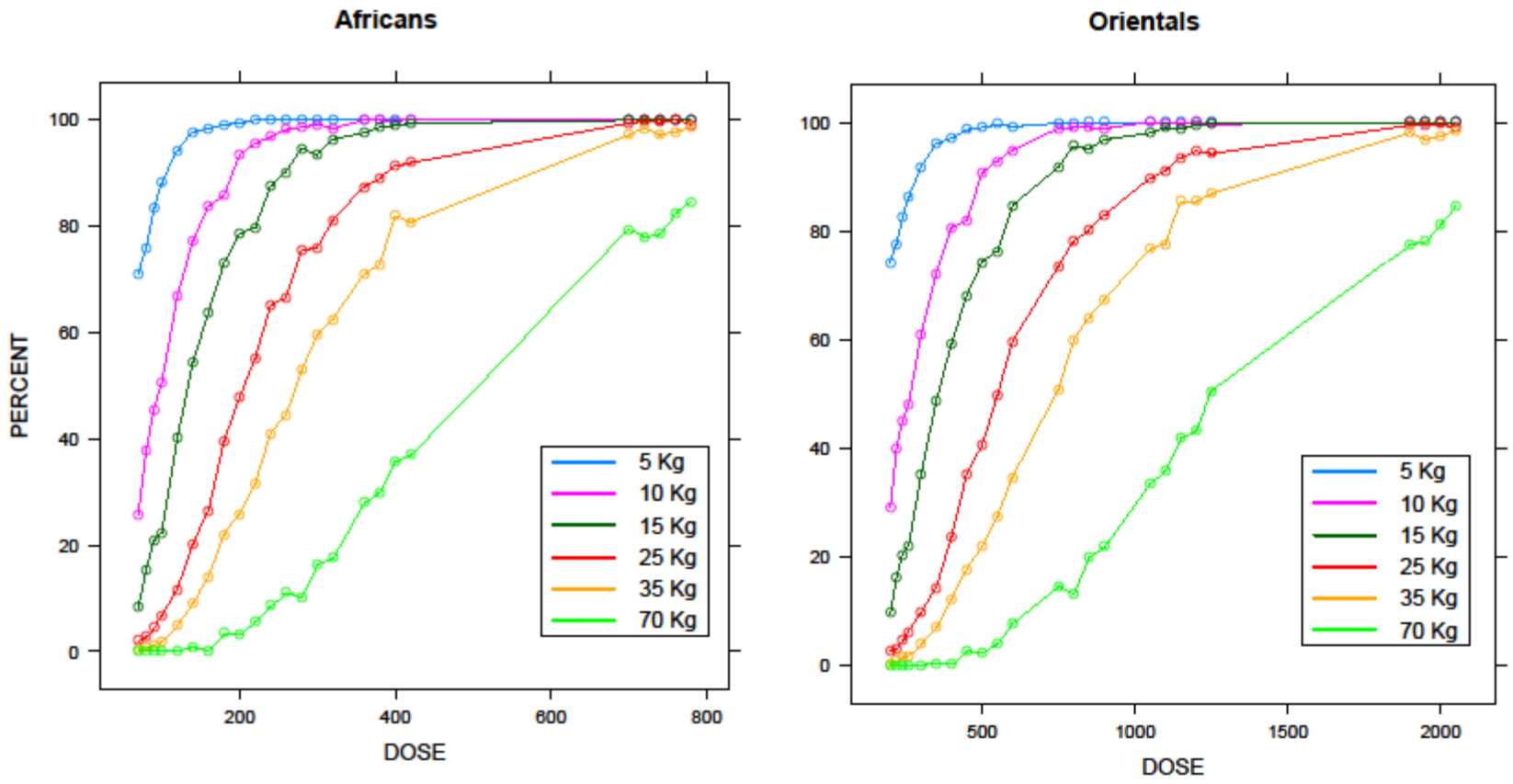
Simulation Scenarios & Dosing Recommendation

Paediatric dosing recommendations were proposed based on pooled data analysis – The correlations between parameters and covariates in the adult population were not sufficiently accurate to predict the true covariate-parameter relationship in children.
Final PK parameter estimates (Table 1) were used to simulate drug exposure in children across a wide weight range following different doses of ATV and PGN. The dose of each compound and the corresponding dose ratio were then derived taking into account the number of simulations in which target exposure was achieved.

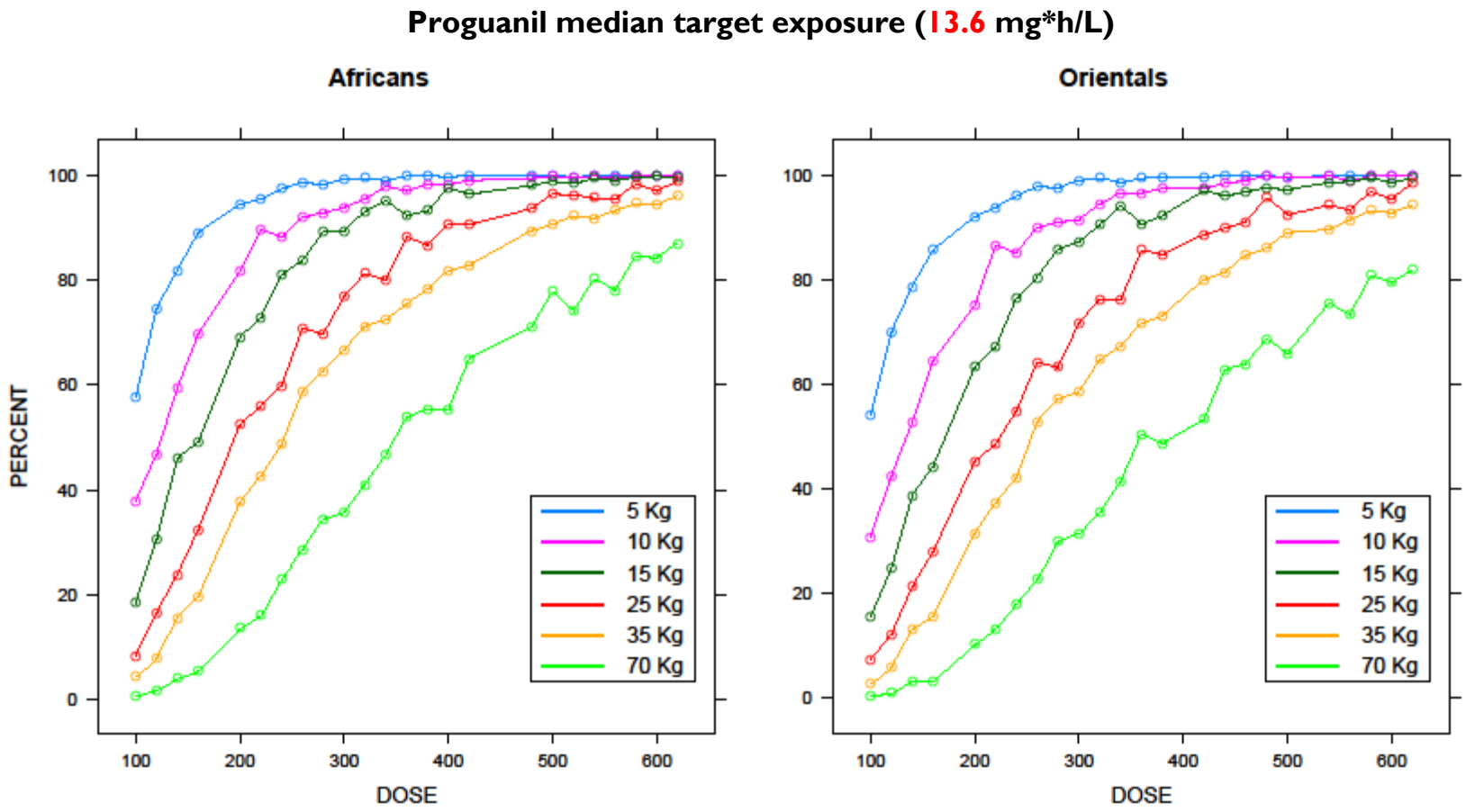
The dosing recommendations for different weight ranges and ethnicities are summarised in the next slides.

Effect of Body weight on Target Exposure

Atovaquone median target exposure (368.7 mg*h/L)



Effect of Body weight on Target Exposure



Dose ratios

Dose required to achieve target exposure						
	Africans			*Orientals*		
Body weight	ATV (mg)	PGN (mg)	**ratio**	ATV (mg)	PGN (mg)	**ratio**
10	160	200	**1 : 1.25**	460	220	**2.1 : 1**
15	240	240	**1 : 1**	640	280	**2.5 : 1**
25	320	320	**1 : 1**	950	360	**2.6 : 1**
35	400	400	**1 : 1**	1100	440	**2.6 : 1**
70	760	580	**1.4 : 1**	2100	580	**3.6 : 1**

Conclusions & Lessons learned

1. The current results clearly show that a model-based approach provides a strong basis for bridging during the development of drug combinations.

2. However, as illustrated by the findings with ATV and PGN, adult data alone may not be sufficiently robust to allow characterisation of parameter-covariate correlations or infer the consequences of differences due to ethnicity, as shown by the significant differences in drug exposure across populations.

3. The empirical evidence of efficacy and safety does not necessarily warrant an accurate rationale for dose selection when bridging concepts can be applied.

Conclusions & Lessons learned

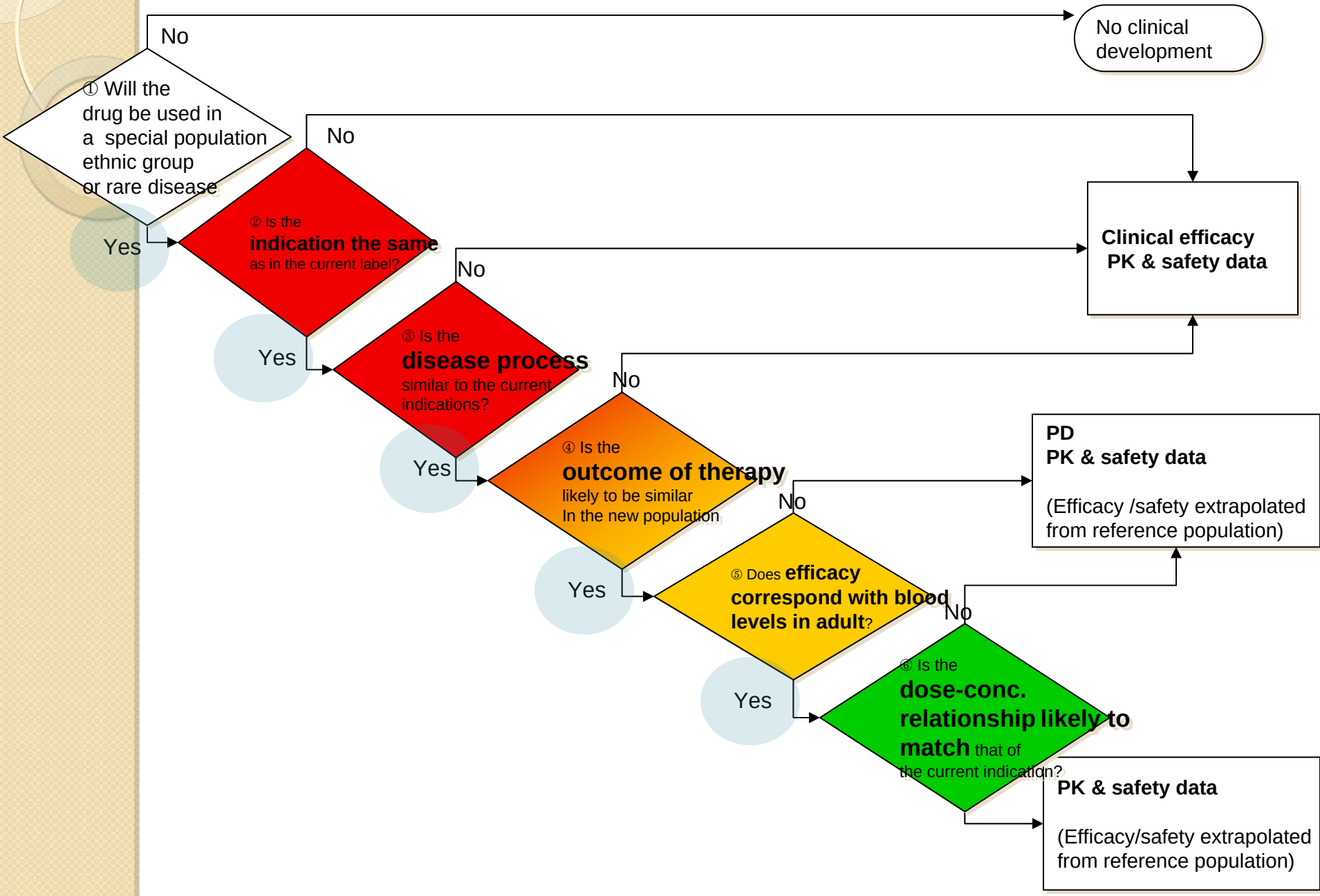
4. The main lesson from this exercise is the need to account for a potential change in the benefit-risk ratio of a treatment when using fixed dose ratios in drug combinations in the presence of interacting covariates.

5. The effect of the interaction between covariates such as body weight, age and ethnicity on drug disposition cannot be assumed constant for different compounds.

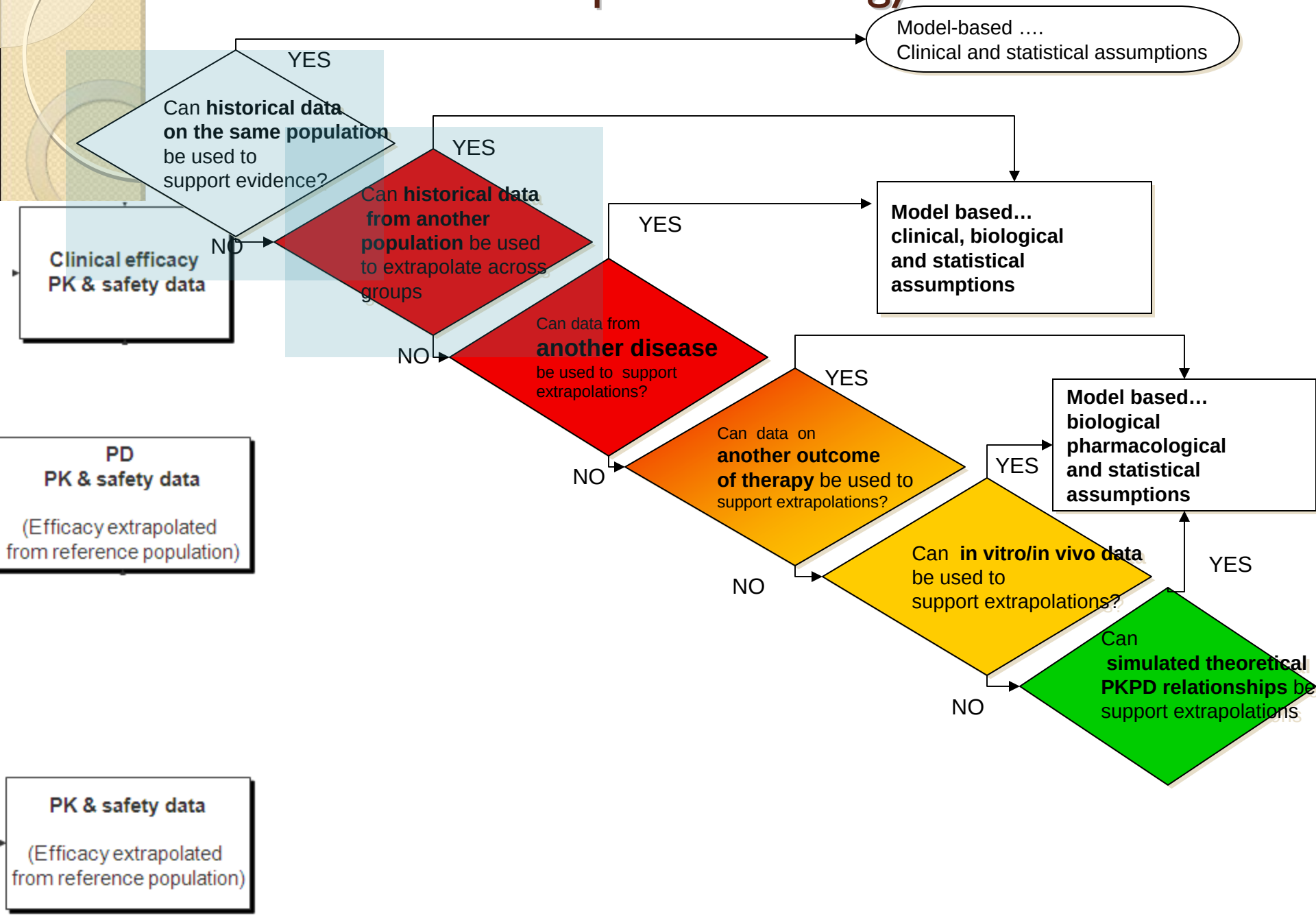
6. Without careful assessment of the differences in pharmacokinetics across populations, inferences made about the efficacy and safety of drug combinations may be biased.

Backup slides

Fixed-dose combination of atovaquone + proguanil



Model-based development strategy



Demographics

- Rich adult and rich children data available (n=783)

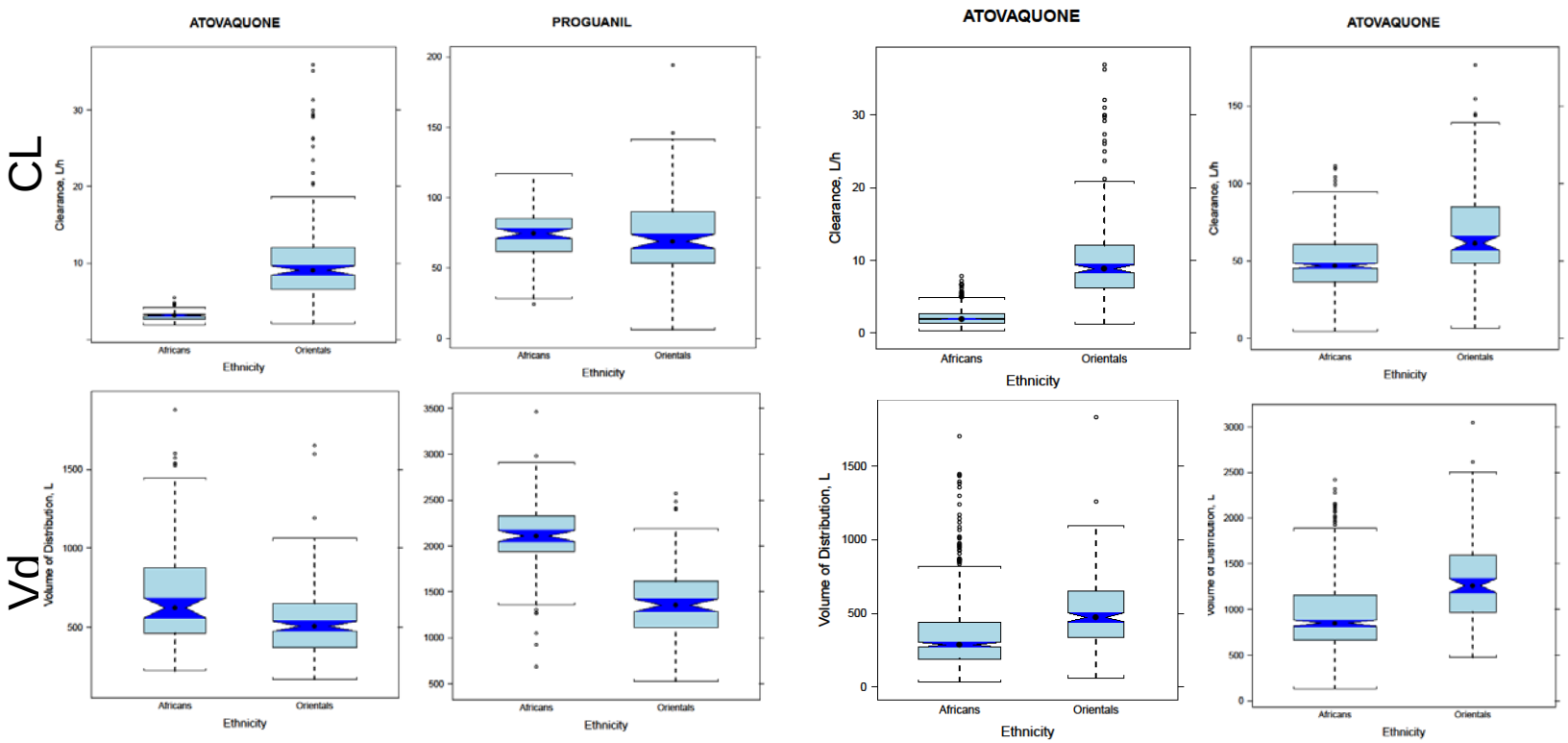
	CHILDREN (mean/range)	ADULTS (mean/range)
Africans	423	106
Orientals	49	150
Malaysians	10	45
Bodyweight (kg)	26.5 (5.4 - 68)	55.6 (39 - 110)
Age (years)	8.8 (0.3 - 17)	29.2 (18 - 65)
Sex (m/f)	247/234	268/33
Blood samples/subject	2.2 (1 - 13)	5.1 (1 - 15)

Summary of modelling results

Table I

	ATV		***PGN***	
Parameters (units)	*mean*	*Bootstrap mean (%CV)*	*mean*	*Bootstrap mean (%CV)*
Fixed effects				
CL/F, Africans (L/h)	3.9	3.9 (6.0)	77.7	77.7 (4.8)
CL/F, Orientals (L/h)	11.7	11.6 (4.7)	83.6	83.7 (81.2)
V/F (L/Kg)	10.4	10.3 (3.8)	-	-
V/F (L)	-	-	1610	1605 (5.7)
KA (/h)	0.24	0.24 (9.7)	1.12	1.13 (7.8)
Exponent on CL	0.801	0.801 (7.5)	0.545	0.542 (13.2)
Exponent on V	-	-	0.640	0.632 (11.5)
Inter-individual variability %				
CL	25.9	25.4 (14.8)	26.0	25.7 (26.5)
V	27.7	27.5 (18.1)	25.1	25.5 (27.3)
KA	94.4	93.6 (8.0)	69.3	70 (22.8)
Steady-state variability	22.6	22.1 (27.6)	21.7	21.5 (26.3)
Non steady-state variability	43.0	42.6 (6.2)	44.9	45.1 (14.0)
Residual error				
Proportional error (%)	33.5	33.3 (5.4)	37.2	37.4 (15.4)
Additive error	0.14	0.14 (23.5)	6.41	6.25 (50.2)

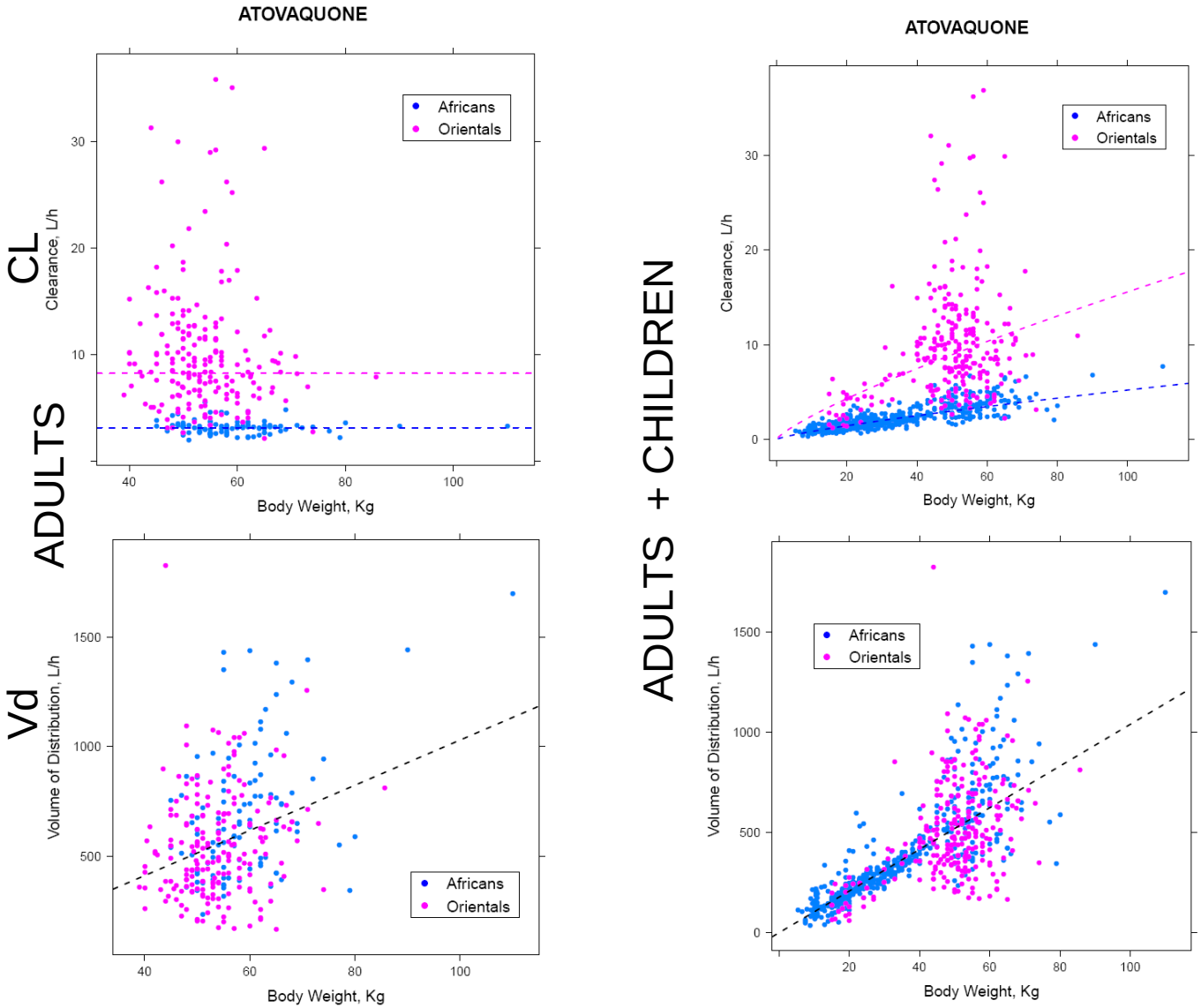
Impact of body weight and ethnicity



ADULTS

ADULTS + CHILDREN

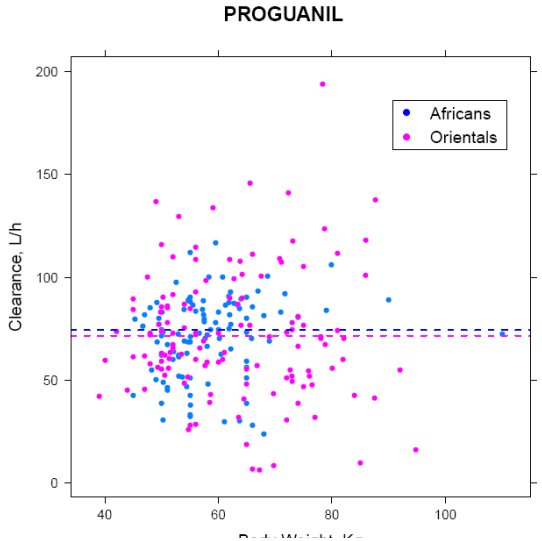
Impact of body weight and ethnicity



Impact of body weight and ethnicity

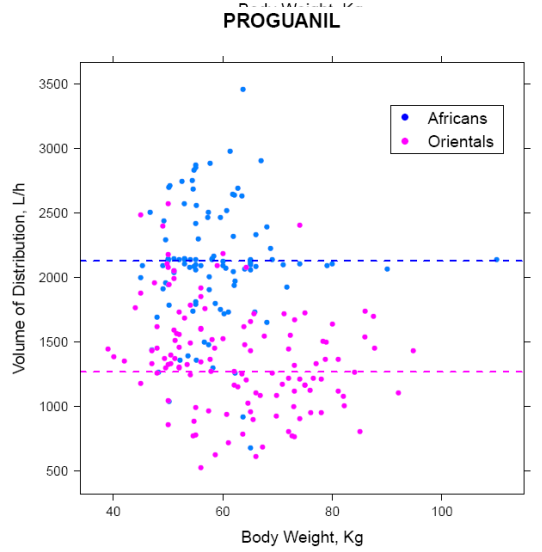
CL

ADULTS

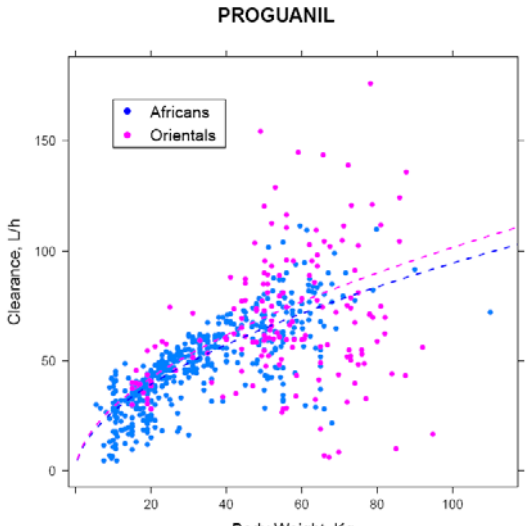


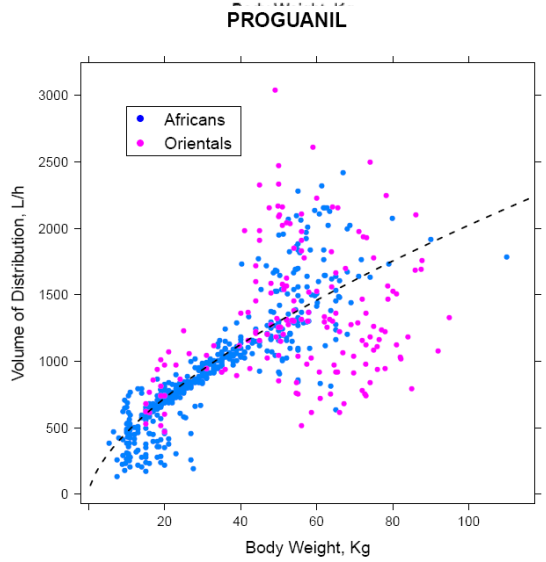
Vd

ADULTS



ADULTS + CHILDREN





Evidence synthesis - Conclusions

Q1 - Could PK in Orientals be predicted from Africans?

94% of the administered dose of ATV is found unchanged in faeces. Hence, there are no obvious reasons for such differences across ethnic groups.
Similar considerations apply to the elimination of PGN, which is primarily excreted by renal processes (60%). The remaining fraction is metabolised by CYP2C19. However, only 15-20% of Orientals is known to show poor metabolism.

Q2 - Could PK in children be predicted from adult data in both ethnic groups?

Assuming data from both ethnic groups were available in adults, PK modelling shows only the effect of ***ethnicity on CL*** *of ATV and PGN. The influence of body* ***weight*** *was observed* ***solely on Vd*** *of ATV. Hence, prediction of PK in children would require the use of priors or empirical scaling by allometric methods.*

Evidence synthesis – Conclusions

Q3 – How well does an allometric model predict PK in children?

In contrast to a fixed allometric exponent of 0.75 for CL, for PGN the estimated exponent values were 0.545 and 0. 64, respectively for CL and Vd. Minor differences between theoretical and observed values for ATV.

Q4 – Can PK differences in children and across ethnic groups be characterised by sampling from a limited group of subjects instead of evaluating drug properties in a full scale trial?

Yes. The use of nonlinear mixed effects modelling shows that PK parameters can be accurately estimated in a small group of children, if priors from the reference population are incorportated into the analysis.

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References

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