

Disposition of artesunate and mefloquine after administration as FDC to adult Thai healthy volunteers and uncomplicated falciparum malaria patients

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1) *USM, Penang, Malaysia*

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(deceased)*

3) *DNDi, Geneva, Switzerland*

4) *CRP-Sant , Luxembourg*

5) *WHO/TDR, Geneva, Switzerland*

BACKGROUND

AS 4
mg/kg

AS 4
mg/kg

AS 4
mg/kg

MQ 15
mg/kg

MQ 10
mg/kg

AS 4
MQ 8
mg/kg

AS 4
MQ 8
mg/kg

AS 4
MQ 8
mg/kg

CURRENT loose
or co-blister
✓ Well researched
✓ Highly effective
✓ Impractical

**NEW fixed
dose**

✓ popPK of the
split dose

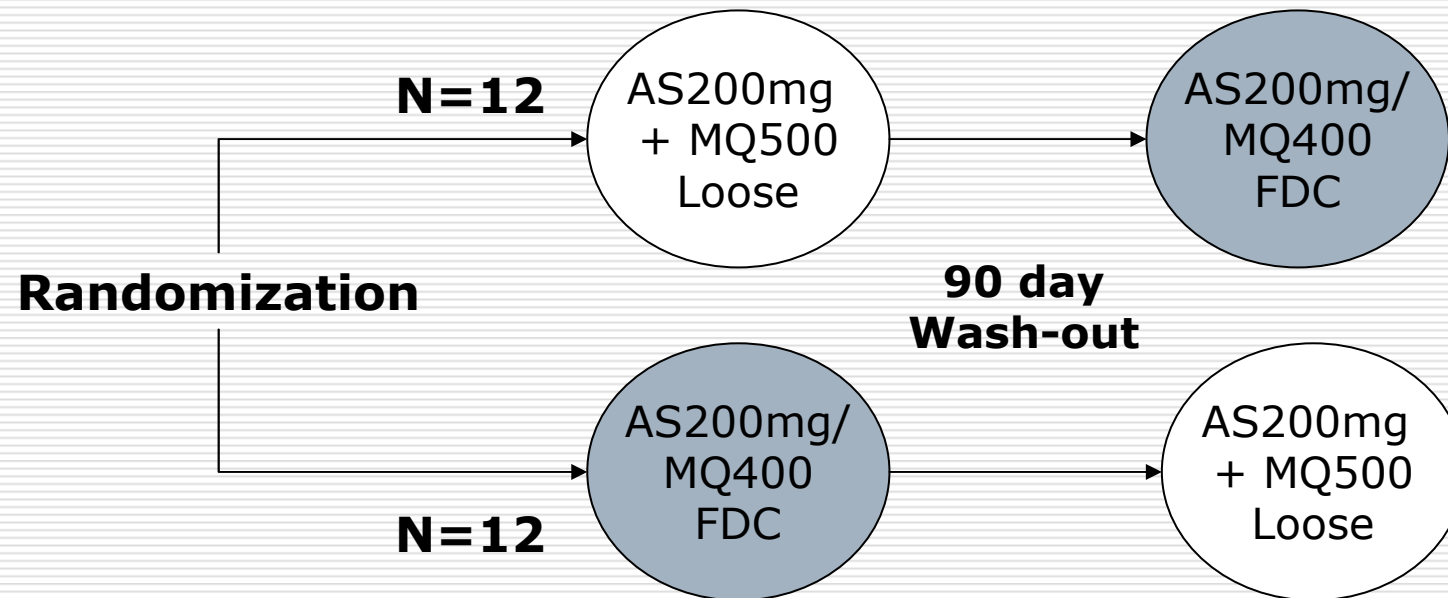
0h

24h

48h

STUDY DESIGN

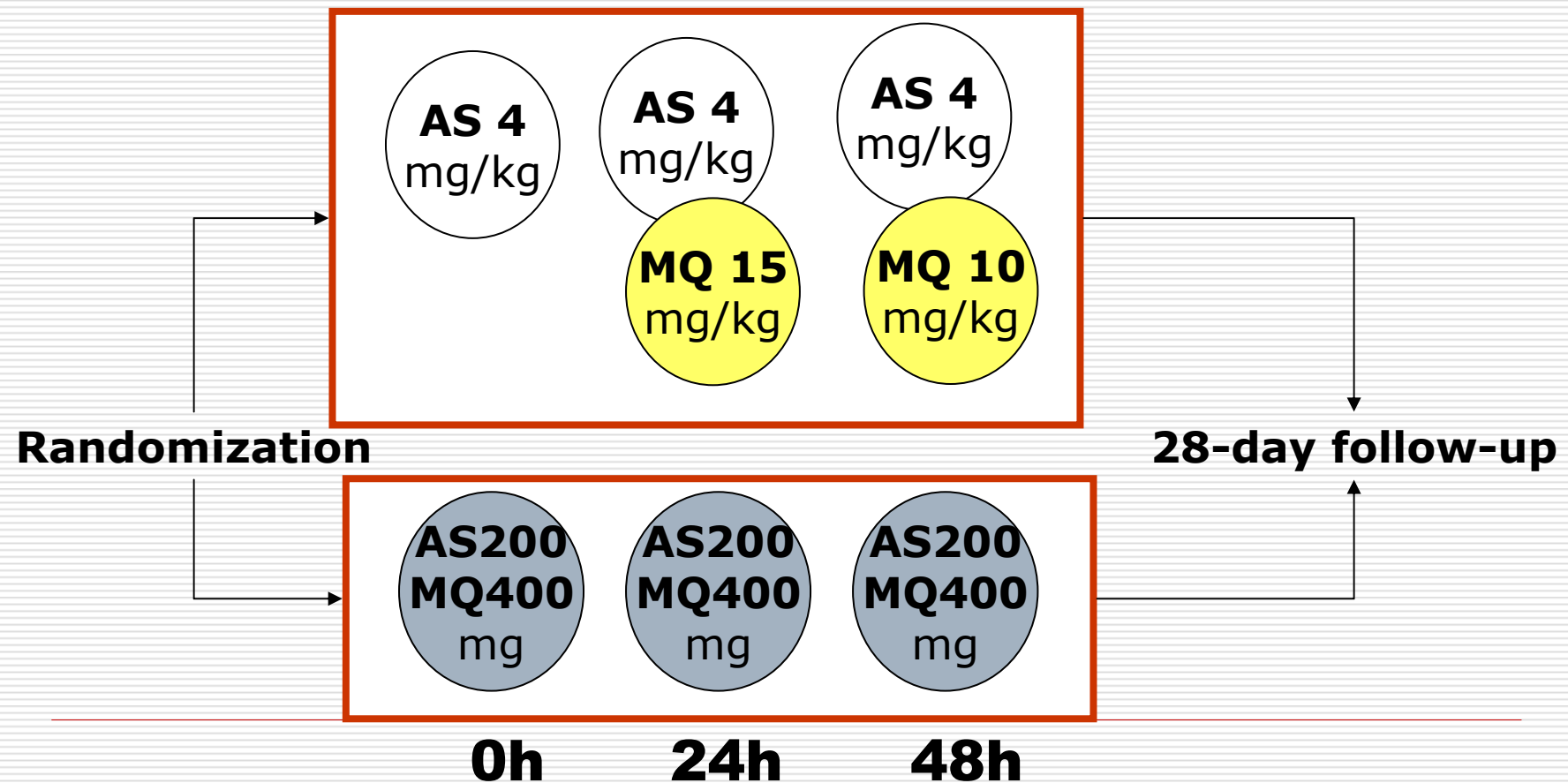
HNVs randomised, 2x2 cross-over



F = Fixed combination; NF = loose combination

STUDY DESIGN

Patients: randomised, parallel arms



METHODOLOGY

SAMPLING TIMES

		0-12h	24h	48h	72h	D5	D7	D14	D28	D56	D70	D90
HNVs	AS/DHA	<input checked="" type="checkbox"/>										
	MQ	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
patients	AS/DHA	<input checked="" type="checkbox"/>										
	MQ	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>			

METHODOLOGY - Assay

- Single extraction procedures with 2 separate determinations for
 - AS/DHA = HPLC-ECD (LoQ = 10ng/0.5ml)
 - MQ = HPLC-UV (LoQ = 25ng/0.5mL)

~~[Lai CS et al, JChromB, 857 (2007): 308]~~

METHODOLOGY – Stats 1

- Drug disposition: mean +/- std deviation
- Plasma profiles: mean +/- SEM vs. time
- Bioavailability: compared as mean AUC_{0-t} and C_{max} of F vs NF.
 - HNV 2x2 Cross-Over design: ANOVA with time, treatment & carry-over effect
 - Patients Parallel design: t-test for independent groups. In case of unequal variances, Mann-Whitney independent rank sum test was

METHODOLOGY – Stats 2

- AUC_{0-t}, C_{max} : parametric 90% CIs of the logarithm of bioavailability ratios (F/NF)
 - Schuirmann's two one-sided tests (TOST)
 - T_{max}: non-parametric Mann-Whitney independent rank sum test for independent samples
-

RESULTS - 1

Fixed-dose coformulation

	DHAeq		MQ	
	HNV	Patients	HNV	Patients
N	24	22	24	22
dose administered (mg)	200mg AS sd	200mg AS/d * 3d	400mg sd	400mg/d * 3d
actual dose received (mg/kg)	3.68 (0.59)	4.02 (0.56)	7.36 (1.19)	24.13(3.34)
Cmax (ng/ml)	733 (295)	1291 (865)	716 (217)	3279 (1252)
Tmax (hr)	1.46 (0.83)	1.9(1.1)	24 (25)	72 (19)
AUCo-t (ng·hr/ml)	1798 (734)	3209 (2435)	322336 (113891)	838253 (376737)
T1/2 (hr)	1.85 (1.60)	1.1 (0.4)	485 (123)	286 (128)
time to [MQ] <500ng/mL			155 (143)	602 (112)

RESULTS - 2

Loose combination

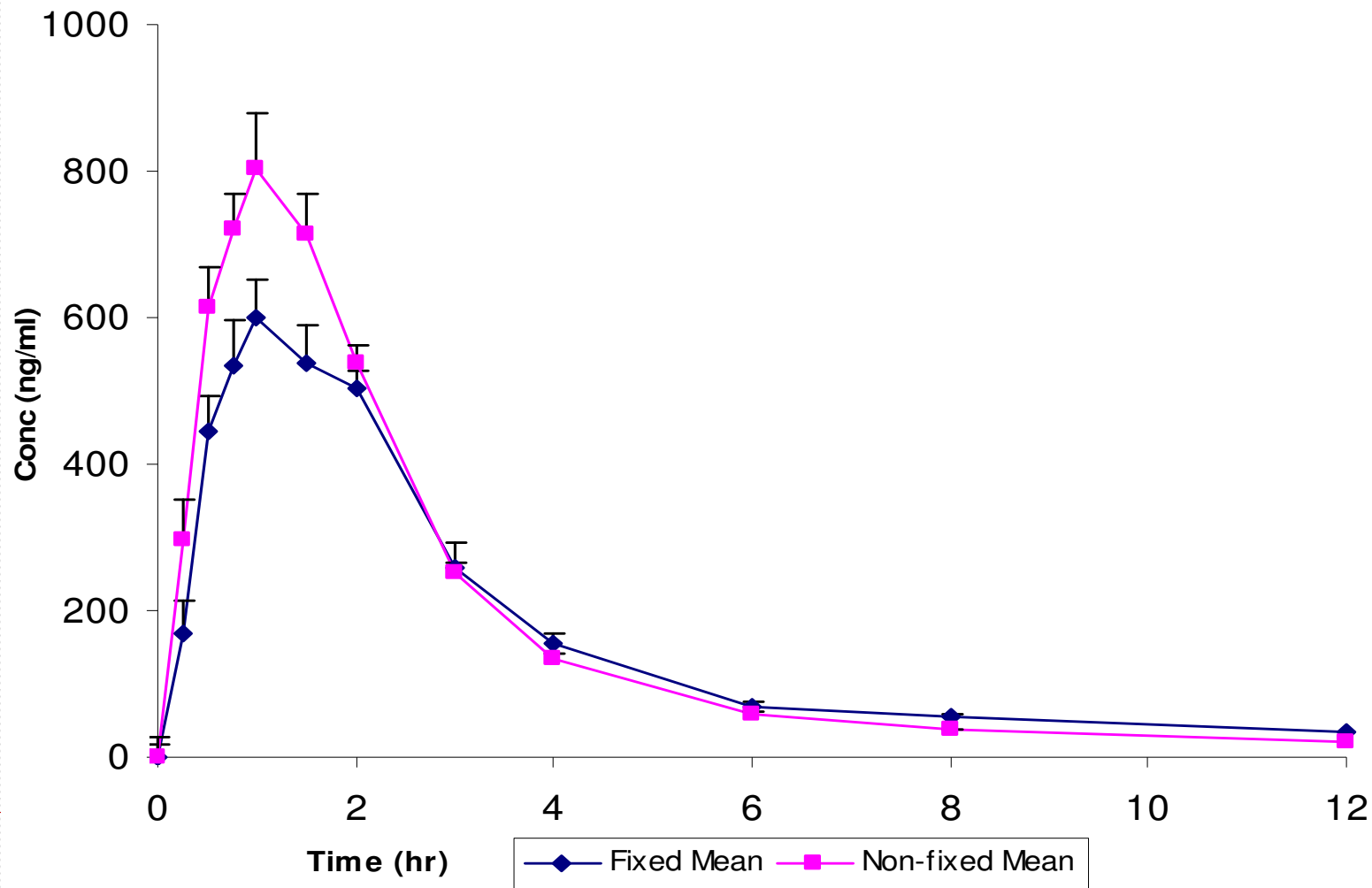
	DHAeq		MQ	
	HNV	Patients	HNV	Patients
N	24	23	24	23
dose administered (mg)	200mg AS sd	4mg/kg/d * 3d	500mg sd	25mg/kg total dose
actual dose received (mg/kg)	3.68(0.59)	4.09 (0.38)	9.21 (1.49)	25.13 (0.42)
Cmax (ng/ml)	979 (363)	2214 (1108)	1284 (318)	3239 (734)
Tmax (hr)	0.9 (0.3)	1.3 (0.7)	5.5 (6.0)	71 (13.5)
AUCo-t (nghr/ml)	2070 (647)	3773 (1469)	481369 (137624)	815716 (230030)
T1/2 (hr)	1.6 (0.6)	0.7 (0.2)	531 (160)	322 (114)
time to [MQ] <500ng/mL			318 (227)	418 (274)

RESULTS - 3

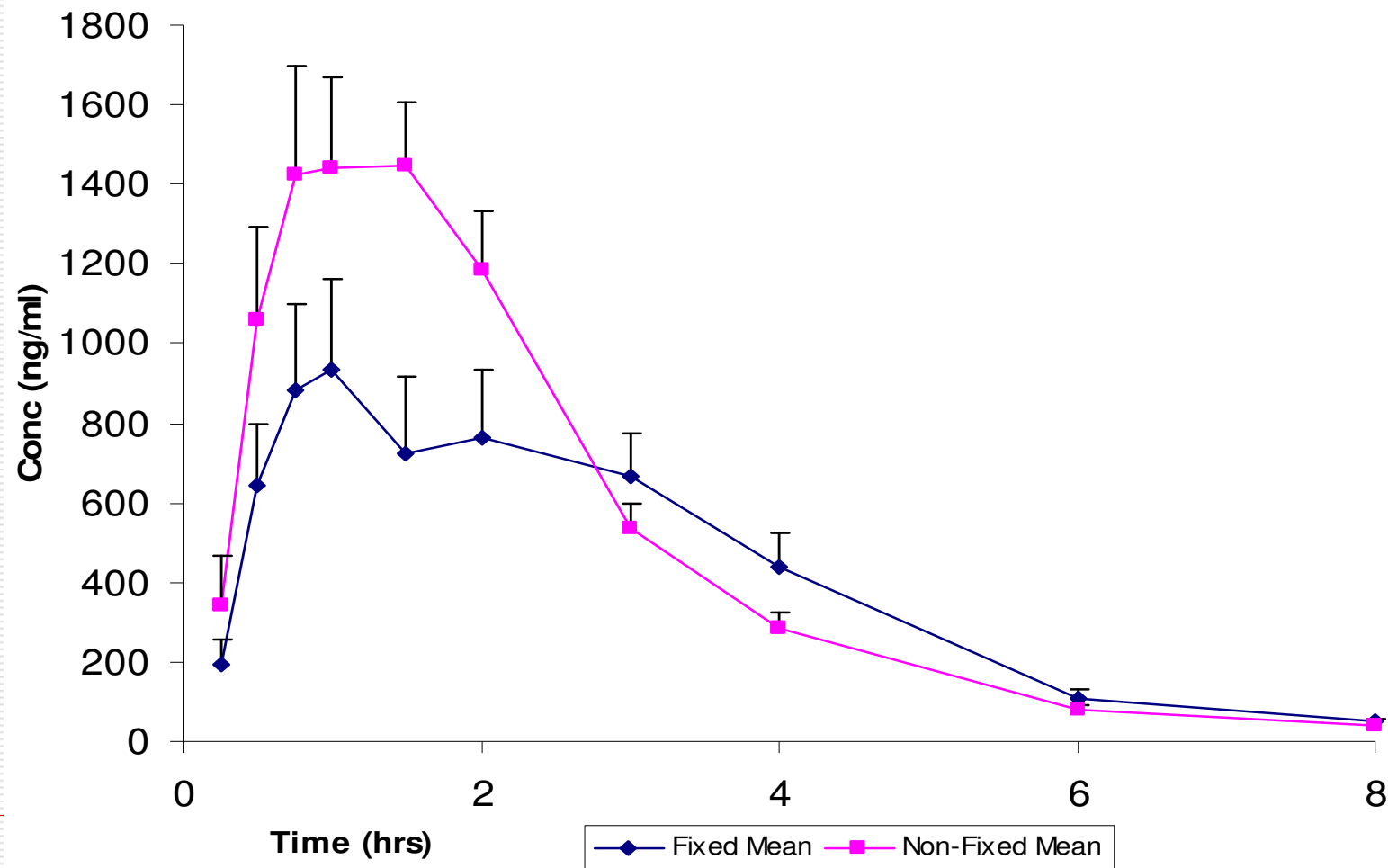
[80 -125%] 90%CI FOR BIOEQUIVALENCE

		HNVs		Patients	
		means ratio	90%CI	means ratio	90%CI
DHAeq	Cmax	0.7271	[57.73 ; 91.58]%	0.5788	[41.36 ; 80.98]%
	AUCo-t	0.8410	[72.15 ; 98.03]%	0.8011	[61.11 ; 105.00]%
MQ	Cmax	0.5981	[49.70 ; 60.82]%	0.9724	[82.94 ; 114.00]%
	AUCo-t	0.6592	[59.76 ; 72.72]%	0.9726	[80.34 ; 117.73]%

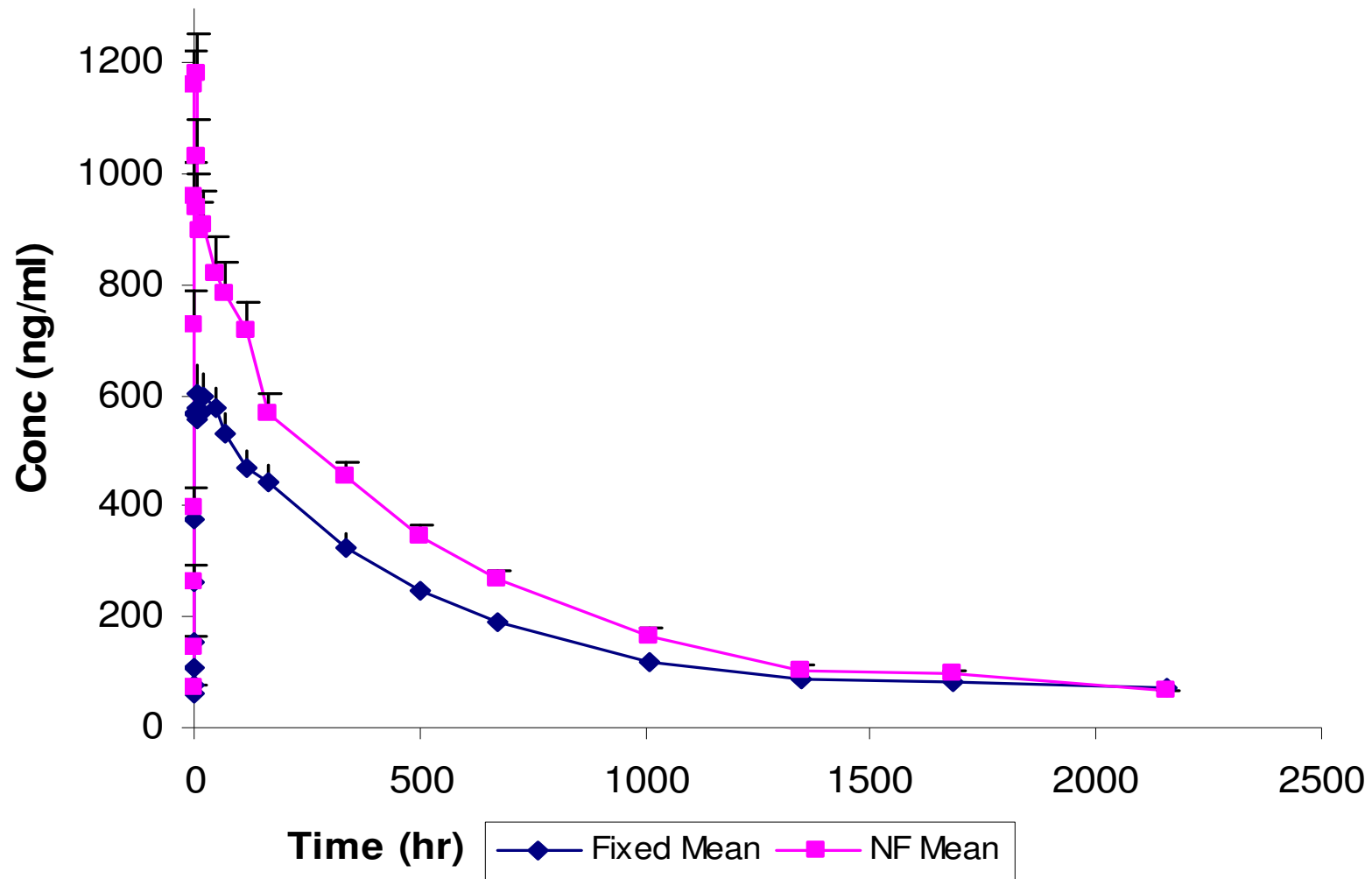
Disposition of DHA-equivalents after single administration of AS as FDC or loose with MQ to THAI ADULT VOLUNTEERS (HNVs)

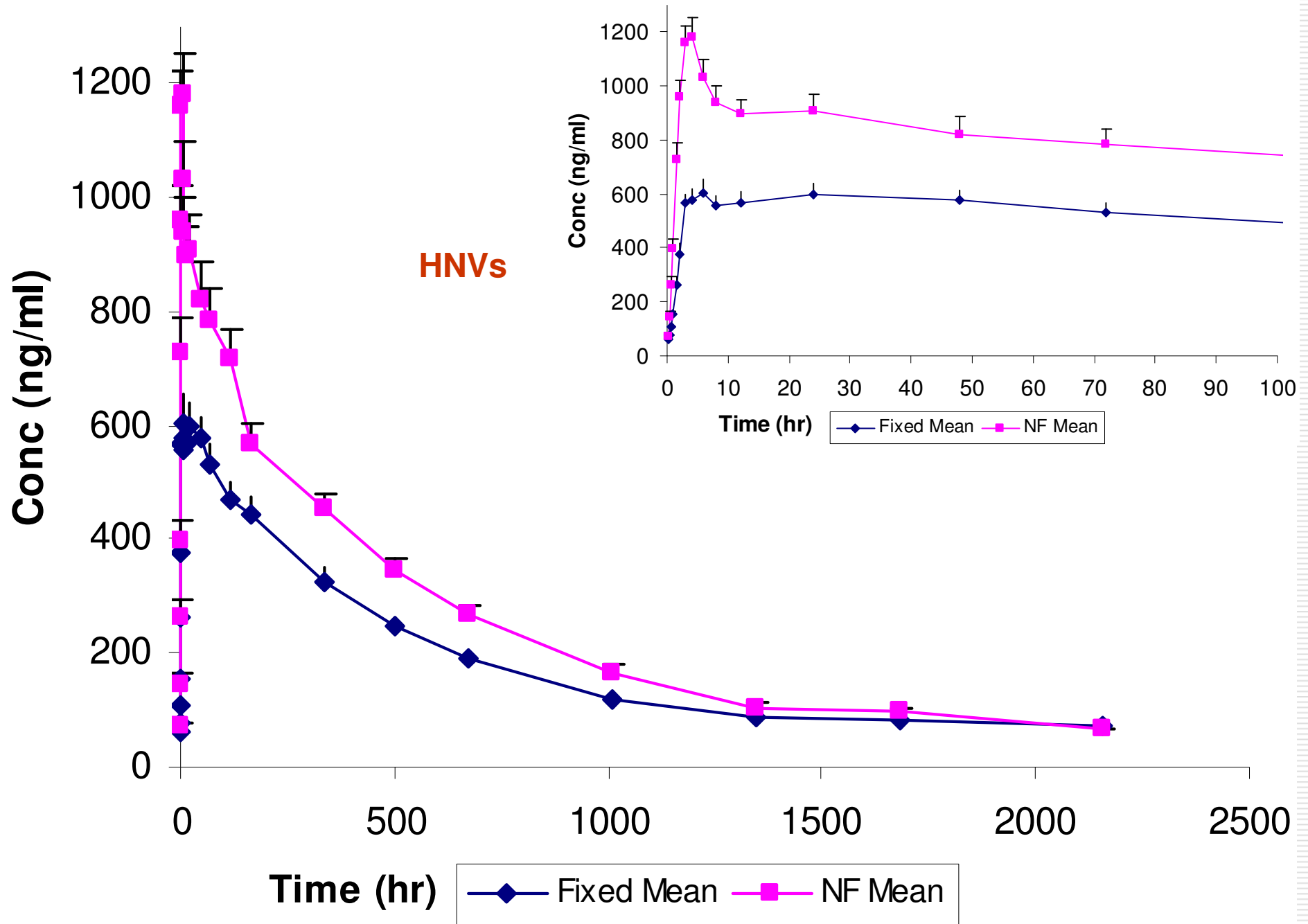


Disposition of DHA-equivalents after single administration of AS as FDC or loose with MQ to MALARIA PATIENTS

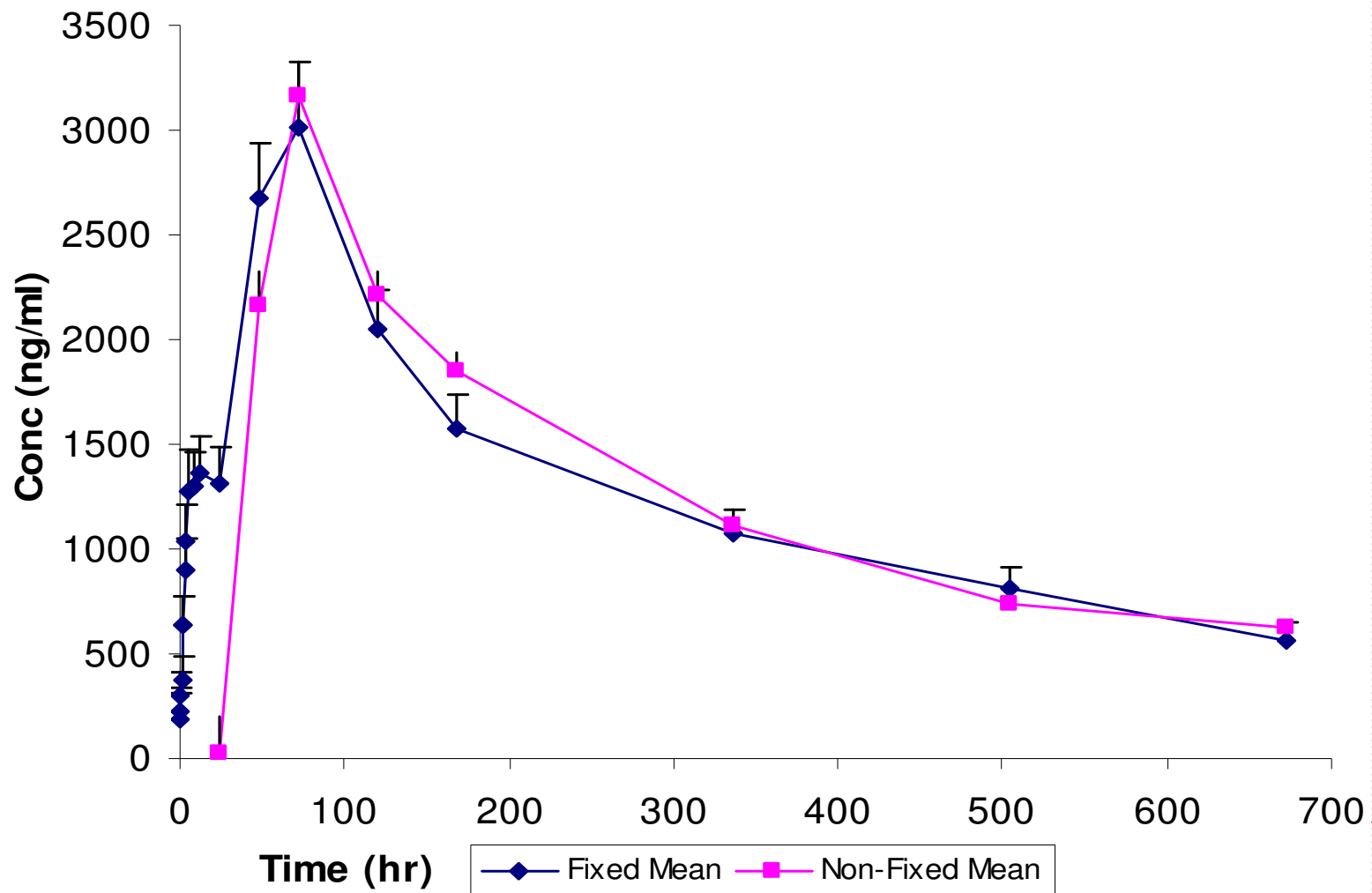


Predicted profile for MQ 8MKD*3D in FDC and MQ15+10MKD at 24,48H as loose combination with AS (MALARIA PATIENTS)





Predicted profile for MQ 8MKD*3D in FDC and MQ15+10MKD at 24,48H as loose combination with AS (MALARIA PATIENTS)



MQ disposition in Healthy volunteers vs. Malaria patients

			Cl/kg (ml/min)	VD/kg (L)	Cl/VD ratio
HNV	FDC	mean	0.35	14.15	0.03
		SD	0.11	4.57	0.01
	Loose	mean	0.31	13.74	0.02
		SD	0.07	3.95	0.01
Pts	FDC	mean	0.41	9.10	0.05
		SD	0.17	2.90	0.02
	Loose	mean	0.40	11.20	0.04
		SD	0.12	5.80	0.01

- Apparent clearance in HNVs 75–80% of patients
- Apparent volume of distribution in HNVs 20–50% higher than patients
- Cl/VD ratio in HNVs 50–60% of patients

CONCLUSIONS

- Adult healthy volunteers (single administration): similar profiles but products not bioequivalent
- Adult malaria patients:
 - similar exposure for MQ (products bioequivalent) and less for AS/DHA with F
 - MQ levels >500 ng/mL for longer with F combination
- Differences probably biologically not relevant
- Higher exposure to both drugs in patients than healthy volunteers confirmed