

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Dondorp AM, Nosten F, Yi P, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med 2009;361:455-67.

## SUPPLEMENTAL TABLES AND FIGURE

**Table S1.**

Baseline characteristics of patients recruited in Pailin according to age group (children <16 years versus adults). Numbers are mean (95% CI) unless otherwise stated. \* Mann-Whitney U test; † median (range); †† geometric mean (95% CI). AS7 is artesunate 2mg/kg/day for 7 days. MAS3 is artesunate 4mg/kg/day for 3 days, followed by mefloquine 15mg/kg on day 3 and 10 mg/kg on day 4 after admission.

	Adults		Children		p-value Adults v children
	AS7 (n=15)	MAS3 (n=14)	AS7 (n=5)	MAS3 (n=6)	
Male, n (%)	11 (73.3)	13 (92.9)	4 (80)	3 (50)	0.23
Weight, kg	49.9 (46.3, 53.4)	50.8 (47.5, 54.0)	29.8 (17.6, 42.0)	26.3 (21.9, 30.7)	<0.001
Age, yrs	31.3 (24.9, 37.8)	25.8 (19.5, 32.0)	12.4 (9.0, 15.8)	11.8 (9.5, 14.2)	<0.001*
Temperature, °C	38.4 (38.0, 38.9)	38.5 (38.0, 39.0)	38.9 (37.5, 40.2)	38.4 (37.5, 39.4)	0.62
Hemoglobin, g/dL	12.0 (10.7, 13.4)	13.0 (12.1, 14.0)	11.4 (9.5, 13.2)	9.6 (7.3, 11.8)	0.001
White blood cells, 1000/uL†	5.3 (3.7, 8.9)	6.0 (3.3, 11.9)	5.2 (3.7, 8.5)	6.7 (3.6, 8.9)	0.65*
Platelets, 1000/uL†	80 (17, 357)	98.5 (40, 181)	92 (42, 209)	130 (58, 383)	0.20*
Glucose, mg/dL†	99.0 (74, 186)	96.5 (74, 184)	96 (89, 105)	98 (87, 169)	0.79*
Creatinine, mg/dL	0.95 (0.86, 1.04)	0.96 (0.85, 1.08)	0.58 (0.52, 0.64)	0.43 (0.35, 0.52)	<0.001*
Bilirubin, g/dL††	1.62 (1.30, 2.02)	1.61 (1.25, 2.07)	1.29 (0.73, 2.28)	1.48 (0.93, 2.35)	0.32
ALT, u/L†	26 (8, 76)	17.0 (6, 40)	22 (11, 80)	15 (11, 22)	0.23*
AST, u/L†	47 (30, 149)	38.0 (34, 65)	43 (36, 145)	36 (29, 44)	0.30*
Alk. Phos., u/L†	85 (54, 186)	87 (63, 153)	158 (115, 226)	156.5 (102, 268)	<0.001*
Albumin, g/dL	3.4 (3.1, 3.7)	4.0 (3.8, 4.2)	3.6 (3.1, 4.2)	3.5 (3.0, 3.9)	0.51
Parasitemia, /uL ††	66404 (38936, 113251)	77094 (43860, 135509)	57894 (9910, 338211)	44324 (14793, 132808)	0.33
Gametocytes n (% positive)	4 (26.7)	2 (14)	1 (20)	4 (66.7)	0.14

**Table S2.**

Clinical and parasitological responses in Wang Pha and Pailin, excluding children <16 years from the analysis. Outcomes are median (range) unless otherwise stated. AS7 is artesunate 2 mg/kg/day for 7 days. MAS3 is artesunate 4 mg/kg/day for 3 days, followed by mefloquine 15 mg/kg on day 3 and 10 mg/kg on day 4 after admission. PCT=parasite clearance time. FCT-A= time till first recorded temperature below 37.5°C; FCT-B= time till start of the first full 24 hours with a recorded temperature below 37.5°C; <sup>a</sup> median (interquartile range)- includes only patients positive for gametocytes at any time. <sup>b</sup> Wilcoxon Breslow test for equality of survivor functions. <sup>c</sup> p = 0.002 when adjusted for baseline parasitaemia by stratification.

	MaeSot (n=40)		Pailin (n=29)		p-value Wang Pha v Pailin
	AS7 (n=20)	MAS3 (n=20)	AS7 (n=15)	MAS3 (n=14)	
Median PCT (IQR), h	54 (42, 72)	48 (30, 54)	83.9 (54, 102)	84.0 (66, 90)	<0.001 <sup>b,c</sup>
PC50, h	4 (1, 24)	3 (1, 16)	11 (1, 25)	10 (1, 22)	0.003
PC90, h	12 (3, 40)	11 (3, 27)	26 (9, 39)	24 (11, 44)	<0.001
PRR24 (% of admission)	1.1 (0, 54.1)	0.3 (0, 15.0)	21.7 (0.3, 97.2)	13.5 (0.9, 67.6)	<0.001
PRR48 (% of admission)	0 (0, 3.8)	0 (0, 0.5)	0.9 (0, 11.5)	0.9 (0, 1)	<0.001
No. recrudescences (%)	2 (10)	1 (5)	5 (33.3)	1 (7.1)	0.15
Gametocyte duration, days <sup>a</sup>	19 (7, 19)	13 (1, 19)	10 (7, 20)	4 (4, 6)	0.71 <sup>b</sup>
Median FCT-A (IQR), days	1 (1, 2)	1 (1, 2)	2 (1, 2)	1 (1, 2)	0.29 <sup>b</sup>
Median FCT-B (IQR), days	2 (1, 2)	2 (1, 2)	2 (1, 2)	1 (1, 2)	0.89 <sup>b</sup>

**Table S3.**

Adverse events: number (%) of patients experiencing symptoms at least once during antimalarial treatment. \* Cough, pleuritic chest pain, shortness of breath.

	Wang Pha (n=40)		Pailin (n=40)		p	p
	AS7 (n=20)	MAS3 (n=20)	AS7 (n=20)	MAS3 (n=20)	WangPha v. Pailin	AS7 vs MAS3
Dizziness	14	19	6	9	<0.001	0.07
Headache	16	19	17	17	0.75	0.52
Nausea	9	5	15	14	0.001	0.26
Anorexia	10	12	16	11	0.25	0.49
Vomiting	3	2	5	5	0.25	0.78
Diarrhoea	0	0	1	3	0.12	0.62
Itching	0	1	0	1	1.0	0.49
Rash	0	1	0	0	1.0	1.0
Urticaria	0	0	0	1	1.0	1.0
Abdominal pain	5	1	9	11	0.001	0.63
Joint pain	10	14	3	4	<0.001	0.25
Muscle pain	14	15	7	8	0.002	0.65
Palpitations	1	2	2	0	1.0	1.0
Sleepiness	8	13	5	5	0.01	0.25
Confusion	0	0	0	0	-	-
Hearing loss	3	4	2	0	0.15	1.0
Numbness	4	4	3	2	0.55	0.76
Blurred vision	0	3	2	2	1.0	0.43
Fatigue	2	0	13	12	<0.001	0.48
Other*	0	0	5	1	0.03	0.09

**Figure S1.**

Relationship between the summed area's under the time concentration curves of artesunate and DHA and the times to parasite clearance in patients treated with artesunate 2 mg/kg/day for 7 days (AS7; red circles) or 4 mg/kg/day for 3 days followed by mefloquine (MAS3; blue triangles) in Pailin (spearman's rho =0.120, p=0.47, left panel) and Wang Pha (spearman's rho =0.139, p=0.39, right panel).

