A randomized controlled trial of dihydroartemisinin-piperaquine, artemesunate-mefloquine and extended artemether-lumefantrine treatments for malaria in pregnancy on the Thailand-Myanmar border

Supplementary File
# S1 Table. Definition of primary efficacy endpoint by initial species

| Initial species | First recurrence | Pf efficacy - Delivery or day 63 whichever occurred later | Pv efficacy - Delivery or day 63 whichever occurred later |
|-----------------|------------------|----------------------------------------------------------|----------------------------------------------------------|
| Pf              | No               | ACPR                                                     | -                                                        |
| Pf              | Pf               | Fail (PCR needed)                                        | -                                                        |
| Pf              | Pv               | Not censored                                             | -                                                        |
| Pv              | No               | -                                                        | ACPR                                                     |
| Pv              | Pf               | -                                                        | Censored                                                 |
| Pv              | Pv               | -                                                        | Fail                                                     |
| Mixed (Pf+Pv)   | No               | ACPR                                                     | ACPR                                                     |
| Mixed (Pf+Pv)   | Pf               | Fail (PCR needed)                                        | Censored                                                 |
| Mixed (Pf+Pv)   | Pv               | Not censored                                             | Fail                                                     |
| Pm              | Any              | -                                                        | -                                                        |

ACPR: adequate clinical and parasitological response (treatment success), EGA: estimated gestational age, PCR: polymerase chain reaction, Pf: Plasmodium falciparum, Pm: Plasmodium malariae, Pv: Plasmodium vivax.
Footnote: Single *P. malariae* in Jul-2011 included as vivax for this figure only.

**S1 Figure.** Monthly number of pregnant women with malaria enrolled in the study for each malaria species over the study period February 2010 to August 2016
### S2 Table. Dose of each compound given to the participants

| Treatment     | N   | Mean (range) of total dose (mg/kg body weight) |
|---------------|-----|-----------------------------------------------|
| **DP**        | 172 |                                               |
| Dihydroartemisinin | 6·5 (4·7-7·3) |
| Piperaquine   | 52·0 (37·6-58·5) |
| **ASMQ**      | 169 |                                               |
| Artesunate    | 11·8 (9·0-15·8) |
| Mefloquine    | 25·2 (19·7-34·7) |
| **ASMQ – fixed dose** | 121 |                                               |
| Artesunate    | 11·7 (9·0-15·8) |
| Mefloquine    | 25·8 (19·7-34·7) |
| **ASMQ – loose dose** | 48  |                                               |
| Artesunate    | 12·0 (11·5-12·3) |
| Mefloquine    | 23·5 (21·6-25·6) |
| **AL+**       | 170 |                                               |
| Artemether    | 16·1 (11·1-24·2) |
| Lumefantrine  | 96·3 (66·7-145·5) |

AL+: artemether-lumefantrine extended regimen, ASMQ: artesunate-mefloquine, DP: dihydroartemisinin-piperaquine.

* Including one patient with protocol violation (i.e. hyperparasitaemia).
S3 Table. The baseline characteristics of patients with *Plasmodium falciparum* monoinfection

| Baseline characteristic                  | All (n=142) | Mean (SD), Percentage (n), Median (range) |
|----------------------------------------|-------------|------------------------------------------|
| EGA (week)                             |             | DP (n=46)                               | ASMQ (n=52) | AL+ (n=44) |
| 1st                                     | 24.7 (8-4)  | 23.6 (8-2)                              | 25.5 (8-8)  | 24.8 (8-2) |
| 2nd                                     | 50.0 (71)   | 54.3 (25)                               | 42.3 (22)   | 54.5 (24)  |
| 3rd                                     | 38.7 (55)   | 34.8 (16)                               | 46.2 (24)   | 34.1 (15)  |
| Age (years)                            | 26.1 (7-3)  | 25.7 (7-6)                              | 27.0 (6-9)  | 25.4 (7-3) |
| Parity                                  | 1           | 25.4 (36)                               | 19.6 (9)    | 25.0 (13)  | 31.8 (14)  |
|                                         | 2           | 17.6 (25)                               | 17.4 (8)    | 11.5 (6)   | 25.0 (11)  |
|                                         | ≥3          | 57.0 (81)                               | 63.0 (29)   | 65.5 (35)  | 43.2 (19)  |
| Gravidity                               | 0           | 31.7 (45)                               | 30.4 (14)   | 30.8 (16)  | 34.1 (15)  |
|                                         | 1           | 19.7 (28)                               | 23.9 (11)   | 11.5 (6)   | 25.0 (11)  |
|                                         | ≥2          | 48.6 (69)                               | 45.7 (21)   | 57.7 (30)  | 40.9 (18)  |
| Smoking                                 | 25.4 (36)   | 30.4 (14)                               | 23.1 (12)   | 22.7 (10)  |
| Betel nut                               | 53.5 (76)   | 54.3 (25)                               | 55.8 (29)   | 50.0 (22)  |
| Ethnicity                               |             |                                         |             |             |
| Karen                                   | 83.8 (119)  | 84.8 (39)                               | 80.8 (42)   | 86.4 (38)  |
| Burmese                                 | 12.0 (17)   | 10.9 (5)                                | 15.4 (8)    | 9.1 (4)    |
| Others                                  | 4.2 (6)     | 4.3 (2)                                 | 3.8 (2)     | 4.5 (2)    |
| Height (cm)                             | 151.6 (5-3) | 151.9 (4-7)                             | 151.8 (5-9) | 151.1 (5-0) |
| Weight (kg)                             | 52.2 (8-0)  | 52.3 (9-5)                              | 52.3 (6-9)  | 52.1 (7-7) |
| BMI (kg/m²)                             | 22.7 (3-2)  | 22.6 (3-8)                              | 22.7 (2-5)  | 22.8 (3-2) |
| Fever (temperature ≥37.5)               | 46.5 (66)   | 43.5 (20)                               | 46.2 (24)   | 50.0 (22)  |
| Fever (including history of fever)      | 82.4 (117)  | 76.1 (35)                               | 84.6 (44)   | 86.4 (38)  |
| Duration of fever (day)                 | 2 (0-7)     | 1 (0-7)                                 | 2 (0-7)     | 2 (0-7)    |
| Haematocrit (%)                         | 31.1 (4-6)  | 30.2 (4-8)                              | 31.4 (4-7)  | 31.5 (4-4) |
| Anaemia                                 |             |                                         |             |             |
| no anaemia                              | 68.3 (97)   | 58.7 (27)                               | 71.2 (37)   | 75.0 (33)  |
| moderate                                | 31.7 (45)   | 41.3 (19)                               | 28.8 (15)   | 25.0 (11)  |
| severe                                  | 0.0 (0)     | 0.0 (0)                                 | 0.0 (0)     | 0.0 (0)    |
| First recorded malaria in pregnancy    | 88.7 (126)  | 91.3 (42)                               | 80.8 (42)   | 95.5 (42)  |
| Pf parasitaemia (/μL)                   | 8164 (16-207994) | 7159 (16-207994) | 10111 (16-124595) | 8290 (96-120199) |
| Presence of Pf gametocytes              | 15.5 (22)   | 23.9 (11)                               | 9.6 (5)     | 13.6 (6)   |

AL+: artemether-lumefantrine extended regimen, ASMQ: artesunate-mefloquine, BMI: body mass index, DP: dihydroartemisinin-piperaquine, EGA: estimated gestational age, Pf: *Plasmodium falciparum*. 

- Anaemia: no anaemia, moderate, severe
- Presence of Pf gametocytes: presence of Plasmodium falciparum gametocytes.
S4 Table. The baseline characteristics of patients with *Plasmodium vivax* mono-infection

| Baseline characteristic | All (n=353) | Mean (SD), Percentage (n), Median (range) | DP (n=121) | ASMQ (n=112) | AL+ (n=120) |
|-------------------------|------------|-----------------------------------------|------------|---------------|-------------|
| EGA (week)              |            |                                         |            |               |             |
|                         | 26·3 (8·1) | 26·5 (7·9) 26·6 (8·4) 25·9 (8·0)         |            |               |             |
| Trimester               |            |                                         |            |               |             |
| 1st                     | 8·5 (30)   | 6·6 (8) 8·0 (9) 10·8 (13)                |            |               |             |
| 2nd                     | 44·2 (156) | 45·5 (55) 45·5 (51) 41·7 (50)            |            |               |             |
| 3rd                     | 47·3 (167) | 47·9 (58) 46·4 (52) 47·5 (57)            |            |               |             |
| Age (years)             |            |                                         |            |               |             |
|                         | 25·6 (6·7) | 25·6 (6·5) 25·9 (6·6) 25·2 (6·9)         |            |               |             |
| Gravidity               |            |                                         |            |               |             |
| 1                       | 36·0 (127) | 39·7 (48) 28·6 (32) 39·2 (47)            |            |               |             |
| 2                       | 20·1 (71)  | 17·4 (21) 25·0 (28) 18·3 (22)            |            |               |             |
| ≥3                      | 43·9 (155) | 43·0 (52) 46·4 (52) 42·5 (51)            |            |               |             |
| Parity                  |            |                                         |            |               |             |
| 0                       | 42·5 (150) | 44·6 (54) 35·7 (40) 46·7 (56)            |            |               |             |
| 1                       | 19·0 (67)  | 19·8 (24) 22·3 (25) 15·0 (18)            |            |               |             |
| ≥2                      | 38·5 (136) | 35·5 (43) 42·0 (47) 38·3 (46)            |            |               |             |
| Smoking                 | 17·6 (62)  | 14·0 (17) 17·9 (20) 20·8 (25)            |            |               |             |
| Betelnut                | 46·7 (165) | 49·6 (60) 42·0 (47) 48·3 (58)            |            |               |             |
| Ethnicity               |            |                                         |            |               |             |
| Karen                   | 71·4 (252) | 70·2 (85) 71·4 (80) 72·5 (87)            |            |               |             |
| Burmese                 | 22·1 (78)  | 20·7 (25) 24·1 (27) 21·7 (26)            |            |               |             |
| Others                  | 6·5 (23)   | 9·1 (11)  4·5 (5)  5·8 (7)               |            |               |             |
| Height (cm)             | 150·9 (5·4)| 150·9 (5·5) 150·9 (5·2) 150·9 (5·6)     |            |               |             |
| Weight (kg)             | 51·5 (7·4) | 52·3 (7·9) 51·8 (7·6) 50·5 (6·7)         |            |               |             |
| BMI (kg/m2)             | 22·6 (3·0) | 22·9 (3·0) 22·7 (3·1) 22·2 (2·7)         |            |               |             |
| Fever (temperature ≥37·5)| 21·0 (74)  | 20·7 (25) 20·5 (23) 21·7 (26)            |            |               |             |
| Fever (including history of fever) | 59·5 (210) | 63·6 (77) 58·0 (65) 56·7 (68)       |            |               |             |
| Duration of fever (day) | 1 (0·10)   | 1 (0·10)   1 (0·7) 1 (0·10)              |            |               |             |
| Haematocrit (%)         | 32·6 (3·7) | 32·8 (3·6) 32·7 (3·7) 32·2 (3·7)         |            |               |             |
| Anaemia                 |            |                                         |            |               |             |
| no anaemia              | 83·9 (296) | 87·6 (106) 83·9 (94) 80·0 (96)           |            |               |             |
| moderate                | 16·1 (57)  | 12·4 (15) 16·1 (18) 20·0 (24)            |            |               |             |
| severe                  | 0·0 (0)    | 0·0 (0)  0·0 (0)  0·0 (0)                |            |               |             |
| First recorded malaria in pregnancy | 78·5 (277) | 73·6 (89) 83·9 (94) 78·3 (94)       |            |               |             |
| Pv parasitaemia (/µL)   | 54·4 (16·83524) | 576 (16·83524) | 544 (16·29893) | 512 (16·40694) |             |
| Presence of Pv gametocytes | 63·7 (225) | 66·1 (80) 56·3 (63) 68·3 (82)         |            |               |             |

AL+: artemether-lumefantrine extended regimen, ASMQ: artesunate-mefloquine, BMI: body mass index, DP: dihydroartemisinin-piperaquine, EGA: estimated gestational age, *Pv*: *Plasmodium vivax*. 
S5 Table. The baseline characteristics of patients with *Plasmodium falciparum* infection, including both *P. falciparum* mono-infection and co-infection of *P. falciparum* and *Plasmodium vivax*  

| Baseline characteristic                  | All (n=157) | DP (n=50) | ASMQ (n=57) | AL+ (n=50) |
|------------------------------------------|-------------|-----------|-------------|------------|
| EGA (week)                               | 24.7 (8.2)  | 23.0 (7.9)| 25.8 (8.7)  | 24.7 (7.9) |
| Trimester                                |             |           |             |            |
| 1st                                      | 10.0 (16)   | 10.0 (5)  | 10.5 (6)    | 10.0 (5)   |
| 2nd                                      | 51.0 (80)   | 58.0 (29) | 40.4 (23)   | 56.0 (28)  |
| 3rd                                      | 38.9 (61)   | 32.0 (16) | 49.1 (28)   | 34.0 (17)  |
| Age (years)                              | 26.1 (7.1)  | 25.9 (7.6)| 27.1 (6.8)  | 25.0 (7.0) |
| Gravidity                                |             |           |             |            |
| 1                                        | 27.4 (43)   | 22.0 (11) | 24.6 (14)   | 36.0 (18)  |
| 2                                        | 17.2 (27)   | 18.0 (9)  | 12.3 (7)    | 22.0 (11)  |
| ≥3                                       | 55.4 (87)   | 60.0 (30) | 63.2 (36)   | 42.0 (21)  |
| Parity                                   |             |           |             |            |
| 0                                        | 33.8 (53)   | 32.0 (16) | 29.8 (17)   | 40.0 (20)  |
| 1                                        | 19.1 (30)   | 24.0 (12) | 12.3 (7)    | 22.0 (11)  |
| ≥2                                       | 47.1 (74)   | 44.0 (22) | 57.9 (33)   | 38.0 (19)  |
| Smoking                                  | 24.8 (39)   | 30.0 (15) | 24.6 (14)   | 20.0 (10)  |
| Betel nut                                | 52.9 (83)   | 56.0 (28) | 52.6 (30)   | 50.0 (25)  |
| Ethnicity                                |             |           |             |            |
| Karen                                    | 83.4 (131)  | 84.0 (42) | 82.5 (47)   | 84.0 (42)  |
| Burmese                                  | 12.1 (19)   | 10.0 (5)  | 14.0 (8)    | 12.0 (6)   |
| Others                                   | 4.5 (7)     | 6.0 (3)   | 3.5 (2)     | 4.0 (2)    |
| Height (cm)                              | 151.4 (5-4) | 152.1 (4-8)| 151.5 (6-0) | 150.5 (5-3) |
| Weight (kg)                              | 52.2 (8-0)  | 52.8 (9-3) | 52.4 (7-0)  | 51.4 (7-8) |
| BMI (kg/m²)                              | 22.8 (3-1)  | 22.8 (3-7) | 22.8 (2-6)  | 22.7 (3-0) |
| Fever (temperature ≥37.5)                | 45.9 (72)   | 40.0 (20) | 43.9 (25)   | 54.0 (27)  |
| Fever (including history of fever)       | 82.2 (129)  | 74.0 (37) | 84.2 (48)   | 88.0 (44)  |
| Duration of fever (day)                  | 2 (0-7)     | 1 (0-7)   | 2 (0-7)     | 2 (0-7)    |
| Haematocrit (%)                          | 31.2 (4-5)  | 30.5 (4-7) | 31.4 (4-6)  | 31.5 (4-3) |
| Anaemia                                  |             |           |             |            |
| no anaemia                               | 69.4 (109)  | 62.0 (31) | 71.9 (41)   | 74.0 (37)  |
| moderate                                 | 30.6 (48)   | 38.0 (19) | 28.1 (16)   | 26.0 (13)  |
| severe                                   | 0.0 (0)     | 0.0 (0)   | 0.0 (0)     | 0.0 (0)    |
| First recorded malaria in pregnancy      | 87.3 (137)  | 88.0 (44) | 79.0 (45)   | 96.0 (48)  |
| Species                                  |             |           |             |            |
| *Plasmodium* mono-infection              | 90.4 (142)  | 92.0 (46) | 91.2 (52)   | 88.0 (44)  |
| *Plasmodium* & *Plasmodium* coinfection  | 9.6 (15)    | 8.0 (4)   | 8.8 (5)     | 12.0 (6)   |
| *Plasmodium* parasitaemia (/µL)          | 8541 (16-207994) | 7159 (16-207994) | 6782 (16-124595) | 9680 (96-120199) |
| *Plasmodium* parasitaemia (/µL)*         | 288 (16-12811) | 104 (16-128) | 1760 (32-6080) | 1296 (16-12811) |
| Presence of *Plasmodium* gametocytes     | 15.3 (24)   | 24.0 (12) | 10.5 (6)    | 12.0 (6)   |
| Presence of *Plasmodium* gametocytes     | 51.3 (8)    | 2.0 (1)   | 53.3 (3)    | 8.0 (4)    |

AL+ : artemether-lumefantrine extended regimen, ASMQ: artesunate-mefloquine, BMI: body mass index, DP: dihydroartemisinin-piperaquine, EGA: estimated gestational age, *Plasmodium falciparum*, Pv: *Plasmodium vivax*.  

* Numbers are among those who had co-infection of *Pv*.  

Mean (SD), Percentage (n), Median (range)
S6 Table. Cumulative proportion of fever and parasite clearance of falciparum and vivax for each treatment arm among pregnant women with history of fever or documented fever at enrolment

|                      | Fever clearance | Parasite clearance |
|----------------------|-----------------|--------------------|
|                      | All             | AL+                | ASMQ               | DP                  | p-value |
| **P. falciparum mono-infection** |                 |                    |                    |                     |         |
| Day 1                | N=116           | N=38               | N=44               | N=34                | 0.29    |
|                      | 74.1% (65.9-91.7) | 71.1% (56.4-84.3) | 81.8% (69.3-91.5) | 67.7% (52.0-82.4)  |         |
| Day 2                | 99.1% (95.6-99.9) | 97.4% (88.2-99.8) | 100%               | 100%                |         |
| Day 3                | 100%            | 100%               | 100%               | 100%                |         |
| **P. vivax mono-infection; N=210** |                 |                    |                    |                     | 0.29    |
| Day 1                | 96.2% (93.0-98.2) | 94.1% (86.8-98.1) | 95.4% (88.3-98.8) | 98.7% (93.8-99.9)  |         |
| Day 2                | 99.1% (96.9-99.8) | 98.5% (93.0-99.9) | 98.5% (92.7-99.9) | 100%                |         |
| Day 3                | 100%            | 100%               | 100%               | 100%                |         |
| **P. falciparum (all)** | N=128           | N=44               | N=49               | N=38                | 0.09    |
| Day 1                | 72.7% (64.8-80.1) | 65.9% (52.0-79.3) | 83.3% (71.6-92.2) | 66.7% (51.4-81.2)  |         |
| Day 2                | 99.2% (96.0-99.9) | 97.7% (89.7-99.9) | 100%               | 100%                |         |
| Day 3                | 100%            | 100%               | 100%               | 100%                |         |
| **P. vivax (all)**   | N=222           | N=74               | N=70               | N=81                | 0.11    |
| Day 1                | 94.1% (90.5-96.7) | 89.2% (80.9-95.0) | 95.7% (89.0-98.9) | 97.5% (92.1-99.5)  |         |
| Day 2                | 99.1% (97.0-99.8) | 98.7% (93.5-99.9) | 98.6% (93.1-99.9) | 100%                |         |
| Day 3                | 100%            | 100%               | 100%               | 100%                |         |

AL+: artemether-lumefantrine extended regimen, ASMQ: artesunate-mefloquine, DP: dihydroartemisinin-piperaquine.
*p-including co-infection of P. falciparum and P. vivax.

Cumulative percentage of women without fever or asexual parasitaemia (95% CI) estimated by Kaplan-Meier method.
S2 Figure. Kaplan-Meier survival curves for antimalarials in pregnancy: Panel a. Recurrence of any malaria species. Panel b. uncomplicated *P. falciparum* in PCR-corrected efficacy censoring intercalated *P. vivax* infection, Panel c. PCR-uncorrected efficacy of antimalarials, and Panel d. *vivax* malaria after falciparum mono-infection. p-values by Wilcoxon test.
S3 Figure. Kaplan-Meier survival curves for parasite clearance of *Plasmodium falciparum* (Panel a) or *Plasmodium vivax* (Panel b) for each treatment arm.
S7 Table. Description of gametocyte carriage, congenital and placental malaria

| Gametocyte carriage |
|----------------------|
| There was no difference in the proportion of patients with gametocytaemia at presentation among the treatment arms either in falciparum or vivax malaria (Table 1). The gametocyte carriage in the 4 weeks after treatment of falciparum malaria was highest for ASMQ 78·3 (95% CI 35·8 to 148·6) per 1000 person-weeks followed by DP 19·2 (2·3 to 69·5) and AL+ 16·4 (2·0 to 59·2), based on very small proportions of patients with gametocytaemia during follow-up (DP 2/104 weeks, ASMQ 9/115 weeks, AL+ 2/122 weeks). |

| Congenital and placental malaria |
|----------------------------------|
| Malaria smears of maternal peripheral blood, cord blood, placental blood, and/or the baby’s peripheral blood were assessed in 76·7% (359/468) of women who had been followed until delivery. Of these 95·3% (342/359) were assessed for at least maternal peripheral blood and baby’s peripheral blood, and 89·4% (321/359) for all four specimens. Rarely, the maternal peripheral smear was positive for *P. vivax* (4·0%, 14/353) or *P. falciparum* trophozoites (0·9%, 3/353). *P. vivax* trophozoites were found in the cord blood in one case (0·3%, 1/329) and the peripheral blood at delivery in another (0·3%, 1/348). In both cases, maternal peripheral blood was negative. Placental blood was positive for *P. falciparum* trophozoites in one case (0·3%, 1/333) and *P. vivax* trophozoites in three cases (0·9%, 3/333) and the maternal peripheral smear was positive for the same species in all of them. All three women with vivax placental malaria had three or four episodes of vivax in pregnancy. The woman with falciparum placental malaria had one vivax (27 days before delivery treated with ASMQ) and no falciparum malaria in her 85 days of follow-up during pregnancy. |
S8 Table. Univariable and multivariable analyses of the risk of PCR-corrected treatment failure in pregnant women with uncomplicated falciparum malaria using a Cox proportional hazard model

| Characteristic                  | Number of failure / assessed | Univariable* | Multivariable |
|--------------------------------|-----------------------------|--------------|--------------|
|                                |                             | HR (95% CI)  | p-value      | HR (95% CI)  | p-value      |
| Treatment                      |                             |              |              |              |              |
| DP                             | 3/49                        | Reference    | Reference    |              |              |
| ASMQ                           | 11/55                       | 3.27 (0.91-11.73) | 0.07        | 3.00 (0.84-10.77) | 0.09        |
| AL*                            | 6/50                        | 1.91 (0.48-7.65)  | 0.36      | 1.85 (0.46-7.40)  | 0.39        |
| Study year (year)              | 20/154                      | 1.20 (0.82-1.76)  | 0.35      |              |              |
| EGA (week)                     | 20/154                      | 1.04 (0.98-1.10)  | 0.19      |              |              |
| Age (year)                     | 20/154                      | 1.07 (1.01-1.13)  | 0.03      | 1.06 (1.00-1.13)  | 0.04        |
| Gravity                        |                             |              |              |              |              |
| 1                              | 3/43                        | 0.47 (0.13-1.67)  | 0.24      |              |              |
| 2                              | 4/26                        | 1.20 (0.38-3.75)  | 0.75      |              |              |
| ≥3                             | 13/85                       | Reference    |              |              |              |
| Height (cm)                    | 20/154                      | 1.08 (0.99-1.17)  | 0.07      |              |              |
| Weight (kg)                    | 20/154                      | 1.03 (0.98-1.09)  | 0.28      |              |              |
| BMI (kg/m²)                    | 20/154                      | 1.02 (0.89-1.18)  | 0.75      |              |              |
| Ethnic group                   |                             |              |              |              |              |
| Karen                          | 16/130                      | Reference    |              |              |              |
| Burmese                        | 4/17                        | 1.89 (0.63-5.67)  | 0.26      |              |              |
| Others                         | 0/7                         | No data      | -            |              |              |
| Fever                          |                             |              |              |              |              |
| no fever                       | 10/69                       | 1.25 (0.52-3.02)  | 0.62      |              |              |
| Days of fever                  |                             |              |              |              |              |
| no fever                       | 10/85                       | Reference    |              |              |              |
| Haematocrit on day 0 (%)       | 20/154                      | 1.04 (0.80-1.37)  | 0.75      |              |              |
| Anaemia                        |                             |              |              |              |              |
| no anaemia                     | 16/106                      | Reference    |              |              |              |
| moderate                       | 4/48                        | 0.58 (0.19-1.75)  | 0.33      |              |              |
| Previous Pf episode            |                             |              |              |              |              |
| no previous Pf                 | 17/141                      | Reference    |              |              |              |
| Species                        |                             |              |              |              |              |
| Pf mono-infection              | 19/139                      | Reference    |              |              |              |
| Pf & Pv coinfection            | 1/15                        | 0.45 (0.06-3.37)  | 0.44      |              |              |
| Presence of gametocytes        |                             |              |              |              |              |
| no gametocytes                 |                             |              |              |              |              |
| Pf parasitaemia (log₁₀µL)      |                             |              |              |              |              |

AL*: extended regimen artemether-lumefantrine, ASMQ: Artesunate-mefloquine, BMI: body mass index, CI: confidence interval, DP: Dihydroartemisinin-pipeline, EGA: estimated gestational age, HR: hazard ratio, Pf: Plasmodium falciparum, Pv: Plasmodium vivax. Global test for proportional-hazard assumption: p=0.34

* Adjusted for treatment groups.
Table. Univariable and multivariable analyses of the risk of PCR-corrected treatment failure in pregnant women with uncomplicated falciparum malaria using a Cox proportional hazard model with \textit{pfkelch13} mutations

| Characteristic | Number of failure / assessed | Univariable* | Multivariable |
|---------------|-----------------------------|--------------|---------------|
|               |                             | HR (95% CI)  | p-value       | HR (95% CI)  | p-value       |
| Age (year)    | 20/154                      | 1.07 (1.01-1.13) | 0.03 | 1.06 (0.99-1.12) | 0.08 |
| Pf parasitaemia (log10/μL) | 20/154 | 1.71 (1.00-2.93) | 0.05 | 1.81 (1.00-3.28) | 0.05 |
| Treatment     |                             |              |               |              |               |
| DP            | 3/49                        | Reference    | Reference     | Reference    | Reference     |
| ASMQ          | 11/55                       | 3.27 (0.91-11.73) | 0.07 | 3.53 (0.97-12.87) | 0.06 |
| AL+           | 6/50                        | 1.91 (0.48-7.65) | 0.36 | 1.78 (0.45-7.14) | 0.41 |
| \textit{pfkelch13}  |                             |              |               |              |               |
| wild type     | 1/43                        | Reference    | Reference     | Reference    | Reference     |
| any mutations | 18/84                       | 12.36 (1.64-93.17) | 0.02 | 13.63 (1.80-102.95) | 0.01 |

AL+: extended regimen artemether-lumefantrine, ASMQ: Artesunate-mefloquine, CI: confidence interval, DP: Dihydroartemisinin-piperaquine, HR: hazard ratio, Pf: Plasmodium falciparum.

* Adjusted for treatment groups.
S4 Figure. Fractional change in haematocrit from baseline during the follow-up for each species (Panel a) or treatment stratified by malaria species (Panel b)
Table. Prevalence of symptoms before and after treatment

| Symptom                        | AL+ (n) | ASMQ (n) | DP (n) | p-value |
|--------------------------------|---------|----------|--------|---------|
| **Day 0**                      |         |          |        |         |
| Headache                       | 78-6%   | 79-9%    | 78-4%  |         |
| Muscle pain                    | 55-4%   | 50-0%    | 55-0%  |         |
| Joint pain                     | 54-2%   | 52-1%    | 53-2%  |         |
| Abdominal pain                 | 19-1%   | 22-5%    | 20-5%  |         |
| Anorexia                       | 41-3%   | 47-9%    | 42-7%  |         |
| Nausea                         | 33-3%   | 30-8%    | 35-1%  |         |
| Vomit                          | 16-7%   | 20-7%    | 17-5%  |         |
| Itchiness                      | 8-9%    | 11-8%    | 9-9%   |         |
| Rash                           | 4-8%    | 4-7%     | 4-7%   |         |
| Urticaria                      | 0-0%    | 0-6%     | 0-0%   |         |
| Dizziness                      | 66-1%   | 58-6%    | 62-0%  |         |
| Hearing abnormality            | 4-8%    | 1-8%     | 7-0%   |         |
| Abnormal vision                | 8-9%    | 7-1%     | 10-5%  |         |
| Diarrhoea                      | 3-0%    | 0-6%     | 2-3%   |         |
| Palpitation                    | 34-5%   | 26-6%    | 35-1%  |         |
| Fatigue                        | 45-8%   | 50-9%    | 47-4%  |         |
| Sleep disturbance              | 40-5%   | 36-7%    | 29-8%  |         |
| Confusion                      | 0-0%    | 0-0%     | 0-6%   |         |
| Numbness                       | 19-1%   | 13-6%    | 23-4%  |         |
| Contraction                    | 1-2%    | 1-2%     | 1-2%   |         |
| Absence of fetal movement      | 0-0%    | 1-3%     | 2-0%   |         |
| Vaginal bleeding               | 0-6%    | 0-0%     | 0-0%   |         |
| **Day 1-14**                   |         |          |        |         |
| Headache                       | 13-9%   | 17-7%    | 16-2%  | 0-95    |
| Muscle pain                    | 2-7%    | 2-4%     | 6-5%   | 0-44    |
| Joint pain                     | 3-9%    | 3-7%     | 3-8%   | 1-00    |
| Abdominal pain                 | 5-9%    | 2-3%     | 2-2%   | 0-20    |
| Anorexia                       | 2-0%    | 5-7%     | 3-1%   | 0-40    |
| Nausea                         | 4-5%    | 13-7-1617| 2-7%   | 0-04    |
| Vomit                          | 0-7%    | 13-4%    | 1-4%   | <0-0001 |
| Itchiness                      | 2-6%    | 0-7%     | 1-3%   | 0-52    |
| Rash                           | 1-9%    | 0-0%     | 0-6%   | 0-13    |
| Urticaria                      | 0-6%    | 0-6%     | 0-0%   | 0-55    |
| Dizziness                      | 5-3%    | 37-1%    | 10-8%  | <0-0001 |
| Tinnitus                       | 1-6%    | 3-8%     | 3-1%   | 0-64    |
| Hearing abnormality            | 0-0%    | 0-0%     | 0-0%   | -       |
| Abnormal vision                | 2-0%    | 0-6%     | 0-0%   | 0-23    |
| Diarrhoea                      | 2-5%    | 1-2-2168| 1-8%   | 0-59    |
| Palpitation                    | 0-9%    | 2-4%     | 0-9%   | 0-63    |
| Fatigue                        | 5-5%    | 2-4%     | 4-5%   | 0-64    |
| Sleep disturbance              | 5-0%    | 14-0%15107| 5-8%  | 0-04    |
| Confusion                      | 0-0%    | 0-0%     | 0-6%   | 1-00    |
| Numbness                       | 0-7%    | 1-4%     | 1-5%   | 0-87    |
| Contraction                    | 1-8%    | 1-2%     | 0-6%   | 0-71    |
| Absence of fetal movement      | 0-7%    | 0-0%     | 0-7%   | 0-78    |
| Vaginal bleeding               | 0-6-1% | 2-4168 | 1-8%   | 0-50    |

AL+: artemether-lumefantrine extended regimen, ASMQ: artesunate-mefloquine, DP: dihydroartemisinin-piperaquine. p-values by Fisher’s exact test.

* Women who had the symptom on day 0 are excluded.
### S11 Table. Description of pregnancy outcomes

| Outcome                  | Description                                                                                                                                                                                                 | Notes                                                                 |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Twins                   | There were three twin pregnancies (one in DP and two in AL+) and among the twins, one of the six newborns were stillborn (in AL+). All twin births are excluded from description of other birth outcomes.               |                                                                    |
| Miscarriage             | There were 280 pregnant women enrolled before 28 weeks of gestation of whom 266 were followed up at least until 28 weeks of gestation: and three miscarriages (1·1%, 3/266), one in each treatment group (1/91 in DP, 1/85 in ASMQ, 1/90 in AL+) (S9 Table). |                                                                    |
| Stillbirth              | Of 462 singleton births (excluding twins, miscarriage and lost to follow-up), five were stillborn (1·1%, 5/462): one in DP (1/155), two each in ASMQ (2/151) and AL+ (2/156) (S9Table).                                         |                                                                    |
| Congenital abnormality  | Five newborns had congenital abnormalities (1·1%, 5/462), three AL+ and two DP. None of these had been exposed to first trimester malaria treatment (S10Table).                                                 |                                                                    |
| Neonatal death          | There were nine neonatal deaths: three AL+, four DP and two ASMQ. Six were related to prematurity (including one due to placental abruption), one resulted from intrapartum asphyxia due to tight nuchal umbilical cord with severe intrauterine growth restriction (2·5th centile), one had a congenital diaphragmatic hernia, and one had meconium aspiration syndrome (10th centile) (S11Table). |                                                                    |
| Preterm birth (PTB)     | The overall proportion of preterm birth was 8·3% (35/423) and was not different among different treatment groups (p=0·45). Treatment was not associated with estimated gestational age at birth by univariable and multivariable linear regression (S12 Table). |                                                                    |
| Small for gestational age (SGA) | Birthweight of 397 (88%) normal live singletons was measured within 72 hours; 26·2% (104) were small for gestational age and proportions were not different among the treatment groups. Length, arm circumference, head circumference at birth and Apgar score at 5 min was also not different among three treatment groups. |                                                                    |
## S12 Table. Details of pregnant women who had miscarriage or stillbirth

| Outcome               | Clinical details of events surrounding birth outcome                                                                 |
|-----------------------|----------------------------------------------------------------------------------------------------------------------|
| **DP group**          |                                                                                                                       |
| Miscarriage           | 18y, G1P0, symptomatic vivax, EGA 12+0, 3 days fever, FHB present on day 3 and discharged. At 13+3 febrile illness, admitted for fever 2 days and treated conservatively – suspected viral illness. EGA 22+2, d77 post DP asymptomatic vivax, treated with chloroquine, day 2 start suprapubic pain and back pain and miscarriage day 3 at EGA 22+4, BW 520g, 300g placenta; FHB lost just before products expelled. |
| Stillbirth –intrapartum | 28y, G6P5, symptomatic falciparum, EGA 20+3, 2 days fever, BT 38·9°C; At EGA 25+3 and 31+3 recurrent asymptomatic vivax. At EGA 35+0 arrived in shock (BP 60/20 mmHg, FHR 108), severe watery diarrhoea (suspected cholera), resuscitated, discharged after 7 days. EGA 35+6 repeat asymptomatic vivax. Three days before labour, she had normal ANC visit. Arrived 38+0, no FHB present, antepartum haemorrhage, placental abruption, post-partum haemorrhage. Normal male, BW 2690g, 16th centile weight for gestation, no maceration, syphilis negative. |
| **ASMQ group**        |                                                                                                                       |
| Miscarriage           | 18y, G2P0, symptomatic falciparum 2·8% iRBC, EGA 7+1, 5 days fever, BT>39°C, plus pyelonephritis, plus stool test revealed hookworm, *Ascaris lumbricoides* and *Trichuris trichuria* [treatment delayed until out of first trimester].FHB present on day of discharge D7. Day 53 vivax malaria 0·3% iRBC EGA 14+5 no FHB detected, treated with chloroquine, plus urine culture for *Escherichia coli*. The miscarriage complete EGA 15+0. |
| Stillbirth –prepartum  | 26y, G3P2, symptomatic vivax (0·5% parasitaemia) EGA 36+6, 7 days fever T 38·4°C; rapidly responded to treatment, clearing her blood stage parasites within 48 hours. The appeared well, ambulatory, FHB normal and due for discharge but became unwell with a rapidly progressive acute respiratory distress syndrome (ARDS) requiring ventilation three days (67 hours) into treatment. Labour was induced in ICU for absent FHB and delivered by forceps, normal BW 2500 g male 49th centile. Ventilatory requirements increased and the patient died on day 7. Concomitant infections (TB, HIV, syphilis) were excluded. |
| And maternal mortality |                                                                                                                       |
| Stillbirth –intrapartum | 19y, G2P0, asymptomatic vivax EGA 11+5, normal ANC care, last seen EGA 38+0 weeks with normal obstetric and physical exam. At EGA 38+3 homebirth, |
with a traditional birth attendant, long labour, lives far and difficult to reach SMRU. Normal male weight not available, no maceration.

| AL+ group | Miscarriage | 40y, G9P8, symptomatic vivax, EGA 15+0, 2 days fever, treatment finished d4, at midnight on day 5, EGA miscarriage 15+4 at 01:30 am [fetus is anencephalic and with an abdominal wall defect]. The patient had a 10% drop in haematocrit but not transfused, oral haematinics only. |
| Stillbirth –prepartum | 33y, G7P5 (4 alive, 1 died 9-month-age fever, 1 miscarriage), symptomatic falciparum (0·1% iRBC), EGA 37+0, 7 days fever BT 38·1°C; rapid recover with treatment. Day 21 no FHB detected at routine ANC care and spontaneous delivery occurred the next day at EGA 40+0. Mother thought baby was moving but at delivery the fetus was macerated indicating fetal death in utero at least 2-3 days previously. Normal BW 2800g female 10th centile for gestation, syphilis negative. |
| Stillbirth –intrapartum | 38y, G6P5, asymptomatic vivax EGA 17+4, smoker since age 7; EGA 31+2 normal obstetric and physical exam, 3 days later presented APH, managed conservatively, next day PPROM, fetal distress, referred in emergency, stillbirth due to placental abruption at EGA 32+0. Normal BW 1600g female 41st centile |

AL+ extended regimen artemether-lumefantrine; ANC antenatal care; ASMQ artesunate-mefloquine; BT body temperature; BW birthweight; DP dihydroartemisinin-piperaquine; EGA estimated gestational age; FHB fetal heart beat; FHR fetal heart rate; G gravidity; iRBC infected red blood cells; P parity; PPROM Preterm premature rupture of the membrane; SMRU Shoklo Malaria Research Unit; TB tuberculosis.
### S13 Table. Details of congenital abnormality and ICD-10 coding

| EGA at exposure | ICD-10 code | Description |
|-----------------|-------------|-------------|
| **DP group**    |             |             |
| EGA 16+1 weeks  | Q37.9       | 33y, G6P4, EGA 34+2, female, BW 1480g, 2nd centile, cleft lip and palate on right side |
| EGA 31+4 weeks  | Q79.0       | 22y, G1P0, EGA 40+2, female, BW 2860g, 12th centile, diaphragmatic hernia confirmed by antenatal ultrasound, was admitted to special care baby unit after birth with a diagnosis of early onset neonatal sepsis and treated but deteriorated rapidly, and died 2 days of life |
| **AL+ group**   |             |             |
| EGA 14+4 weeks  | Q37.9       | 20y, G1P0, EGA 40+0, female, BW 2895g, 16th centile, cleft lip and palate on left side |
| EGA 20+2 weeks  | Q24.9       | 24y, G4P2, EGA 38+4, female, born at home, acyanotic congenital heart disease diagnosed clinically. |
| EGA 31+6 weeks  | Q01.9 and Q70.0 | 40y, G9P8, EGA 33+5, male, BW 2030g, 38th centile, nasofrontal encephalocele and multiple syndactyly |

AL+ extended regimen artemether-lumefantrine; BW birthweight; DP dihydroartemisinin-piperaquine; EGA estimated gestational age; G gravidity; ICD-10 International statistical classification of diseases and related health problems, 10th version; P parity.
| Cause of death                             | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **DP group**                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Respiratory distress, prematurity         | 18y G1P0, PV symptomatic EGA 16+2; reappearance PV symptomatic day 76 treated with CHQ. Day 79 preterm labour at home, NVD EGA 28+1, normal live born female infant weighing 1120g at 02:30am. At daylight they presented and were admitted to the clinic. Baby passed away at 39 hours of active care.                                                                                      |
| Respiratory distress, congenital abnormality | 22y, G1P0, symptomatic PV EGA 31+4, and spontaneous labour at term EGA 40+2, female, BW 2860g, 12th centile, diaphragmatic hernia confirmed by ultrasound, was admitted to special care baby unit after birth with a diagnosis of early onset neonatal sepsis and treated but deteriorated rapidly, and died at 2 days of life.                                      |
| Intrapartum asphyxia with severe IUGR     | 19y, G3P1, symptomatic PV, EGA 35+3, with spontaneous labour at EGA 40+0, NVD, cord around the neck and arm, cord cut on perineum, failed resuscitation stopped at 20 minutes, no spontaneous respiration, male BW 2600g, APGAR score 21 and 45, 2nd-5th centile weight for age.                                                                                                                                                                |
| Meconium aspiration syndrome              | 19y G1P0, PV asymptomatic EGA 22+1, reappearance PV asymptomatic on day 84 and spontaneous labour on day 97 at EGA 40+2, with thick meconium, IUGR 10th centile, BW 2940, APGAR score 41 and 75 and cardio respiratory arrest 6 hours after birth; and could not be resuscitated.                                                                                                                                          |
| **ASMQ group**                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Apnoea of prematurity (placental abruption)| 20y, G3P2, PF symptomatic 2.2% iRBC, EGA 24+2, negative on d6; spontaneous labour on d11, arrived fully dilated, NVD live born 25+1 week normal male infant BW 730 g, APGAR score 11 and 23, who passed away after 70 mins of palliative care. Retained placenta delivered after 30 mins with 50 cc old retroplacental clot.                                                      |
| Apnoea of prematurity                      | 19y, G3P1, labour pain, 2-4% iRBC d46, with spontaneous labour at home, no time to come, EGA 26+3, NVD, live born (weak cry), externally normal, died in <15 minutes.                                                                                                                                                                                                                                                                  |
| **AL+ group**                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Apnoea of prematurity                      | 42y, G7P+2, PV asymptomatic EGA 15+2, reappearance PV symptomatic day 49, treated with CHQ. Day 11 of episode 2 she went into labour at EGA 24+5 (she had mild pneumonia treated with oral amoxycillin and salbutamol inhaler), and NVD, normal live born male BW 600g, APGAR score of 11 and 15, who passed away, 38 mins of palliative care.                                                                 |
| Respiratory distress, prematurity         | 29y G2P1, asymptomatic PV EGA 28+5, discharged well at day 3 but presented 7 days later with pre-term labour with fetal distress; NVD, normal female, EGA 29+4, day 71 preterm labour at home, NVD EGA 29+5, normal live born male infant weighing 1120g at 02:30am. At daylight they presented and were admitted to the clinic. Baby passed away at 39 hours of active care. |
29+6 weeks, BW 1300g, and APGAR score was 1\textsuperscript{1} and 2\textsuperscript{2}, neonatal resuscitation was done but baby passed away after 40 minutes of life.

| Prematurity | 20y G2P1, symptomatic PV EGA 31+4, preterm labour commenced during treatment, dexamethasone (full course) and nifedipine commenced. She became afebrile but NVD, on day 3 while still on malaria treatment, EGA 32+0 weeks, BW 1720g female, APGAR score was 9\textsuperscript{1} and 10\textsuperscript{5}, and admitted to the Special Care Baby Unit, gaining weight and starting to tolerate milk feeds but the mother discharged herself and the baby on day 7. The mother could not be encouraged to return to the clinic. The baby passed away at home on day 12 of life. |

Abbreviations: BW birthweight; CHQ chloroquine; EGA estimated gestational age; G gravidity; iRBC infected red blood cells; IUGR intra-uterine growth restriction; NVD normal vaginal delivery; P parity; PF *Plasmodium falciparum*; PV *Plasmodium vivax*. 
### Table 1. Univariable and multivariable linear regression analyses of the characteristics associated with gestational week at birth among those who had malaria in pregnancy

| Characteristic | N   | Coefficient (95% CI) | p-value | Coefficient (95% CI) | p-value |
|----------------|-----|----------------------|---------|----------------------|---------|
| EGA at malaria episode (week) | 452 | 0.014 (-0.01-0.04) | 0.21    | -1.38 (-2.76-0.002) | 0.05    |
| Age (years)    | 452 | 0.02 (-0.01-0.05)   | 0.15    | Reference            |         |
| Gravity        |     |                      |         |                      |         |
| 1              | 156 | -0.12 (-0.53-0.30)  | 0.58    |                      |         |
| 2              | 86  | -0.23 (-0.72-0.27)  | 0.37    |                      |         |
| ≥3             | 210 | Reference            |         |                      |         |
| Previous history of stillbirth no | 8   | -1.36 (-2.75-0.03)  | 0.06    | -1.38 (-2.76-0.002) | 0.05    |
| Height (cm)    | 452 | 0.04 (0.01-0.07)    | 0.02    |                      |         |
| Weight (kg)    | 452 | 0.03 (-0.01-0.05)   | 0.01    | 0.03 (0.01-0.05)     | 0.01    |
| BMI (kg/m²)    | 452 | 0.05 (-0.01-0.11)   | 0.10    |                      |         |
| MUAC (cm)      | 450 | 0.05 (-0.02-0.12)   | 0.15    |                      |         |
| Ethnic group   |     |                      |         |                      |         |
| Karen          | 342 | Reference            |         |                      |         |
| Burmese        | 82  | 0.38 (-0.10-0.86)   | 0.12    |                      |         |
| Others         | 28  | 0.33 (-0.43-1.10)   | 0.39    |                      |         |
| Smoking        | 90  | -0.28 (-0.74-0.17)  | 0.22    |                      |         |
| non smoker     | 362 | Reference            |         |                      |         |
| Betel nuts use no | 224 | 0.03 (-0.34-0.40)   | 0.87    |                      |         |
| no             | 228 | Reference            |         |                      |         |
| Fever          | 126 | -0.12 (-0.53-0.29)  | 0.57    |                      |         |
| no fever       | 326 | Reference            |         |                      |         |
| Days of fever  | 452 | 0.01 (-0.10-0.12)   | 0.87    |                      |         |
| Haematocrit on day 0 (%) | 452 | 0.016 (-0.03-0.06) | 0.49    |                      |         |
| Anaemia no anaemia | 365 | Reference            |         |                      |         |
| moderate       | 87  | -0.21 (-0.68-0.25)  | 0.36    |                      |         |
| Species        |     |                      |         |                      |         |
| Pf mono-infection | 128 | Reference            |         |                      |         |
| Pv mono-infection | 309 | 0.04 (-0.37-0.45)   | 0.87    |                      |         |
| Pf & Pv coinfection | 14 | 0.30 (-0.79-1.40)   | 0.59    |                      |         |
| Pm mono-infection | 1  | -0.69 (-4.61-3.23)  | 0.73    |                      |         |
| Parasitaemia load lowest | 107 | Reference            |         |                      |         |
| Lower middle   | 112 | 0.06 (-0.46-0.59)   | 0.81    |                      |         |
| Higher middle  | 114 | 0.10 (-0.42-0.63)   | 0.69    |                      |         |
| Highest        | 119 | -0.18 (-0.69-0.24)  | 0.51    |                      |         |
| Treatment      |     |                      |         |                      |         |
| DP             | 152 | Reference            |         |                      |         |
| ASMQ           | 149 | 0.21 (-0.23-0.66)   | 0.35    | 0.26 (-0.18-0.71)    | 0.25    |
| AL+            | 151 | 0.01 (-0.44-0.46)   | 0.96    | 0.08 (-0.36-0.52)    | 0.72    |
| Total number of MiP | 452 | 0.08 (-0.08-0.24)   | 0.34    |                      |         |

AL+: extended regimen artemether-lumefantrine, ASMQ: Artesunate-mefloquine, BMI: body mass index, CI: confidence interval, DP: Dihydroartemisinin-piperazine, EGA: estimated gestational age, MUAC: middle upper arm circumference, Pf: Plasmodium falciparum, Pm: Plasmodium malariae, Pv: Plasmodium vivax.* Adjusted for treatment groups.
### S16 Table. Univariable and multivariable linear regression analyses of the characteristics associated with SGA z-score (birthweight for gestational age and newborn sex at birth)

| Characteristic                        | N    | Univariable*   |         | Multivariable |         |
|---------------------------------------|------|----------------|---------|---------------|---------|
|                                       |      | Coefficient (95% CI) | p-value | Coefficient (95% CI) | p-value |
| EGA at malaria episode (week)         | 397  | 0·002 (-0·01-0·01) | 0·79    | -0·35 (-0·54-0·17) | 0·0002  |
| Age (years)                           | 397  | 0·01 (0·00-0·02)  | 0·15    | 0·06 (-0·16-0·28) | 0·60    |
| Gravity                               |      |                |         |               |         |
| 1                                     | 140  | -0·42 (-0·62-0·23) | <0·0001 | -0·35 (-0·54-0·17) | 0·0002  |
| 2                                     | 78   | 0·02 (-0·21-0·26)  | 0·83    | 0·06 (-0·16-0·28) | 0·60    |
| ≥3                                    | 179  | Reference        | Reference| Reference      |         |
| Previous history of stillbirth no     | 8    | -0·10 (-0·74-0·53) | 0·74    |               |         |
| Height (cm)                           | 397  | 0·03 (0·01-0·05)  | 0·0003  | 0·03 (0·02-0·05) | <0·0001 |
| Weight (kg)                           | 397  | 0·04 (0·02-0·05)  | <0·0001 |               |         |
| BMI (kg/m²)                           | 397  | 0·07 (0·04-0·10)  | <0·0001 | 0·05 (0·02-0·08) | 0·0005  |
| MUAC (cm)                             | 396  | 0·06 (0·02-0·09)  | 0·001   |               |         |
| Ethnic group                          |      |                |         |               |         |
| Karen                                 | 299  | Reference       |         | Reference      |         |
| Burmese                               | 73   | -0·07 (-0·30-0·16) | 0·56    |               |         |
| Others                                | 25   | 0·13 (-0·24-0·50) | 0·49    |               |         |
| Smoking                               | 78   | -0·16 (-0·38-0·06) | 0·16    |               |         |
| non smoker                            | 319  | Reference       |         |               |         |
| Betel nuts use                        |      |                |         |               |         |
| no                                    | 197  | 0·12 (-0·06-0·30) | 0·18    |               |         |
| no fever                              | 200  | Reference       |         |               |         |
| Days of fever                         | 397  | -0·05 (-0·10-0·01) | 0·10    |               |         |
| Haematocrit on day 0 (%)              | 397  | 0·02 (-0·01-0·04) | 0·15    |               |         |
| Anaemia                               |      |                |         |               |         |
| no anaemia                            | 320  | Reference       |         | Reference      |         |
| moderate                              | 77   | -0·32 (-0·54-0·10) | 0·01    | -0·24 (-0·45-0·03) | 0·03    |
| Species                               |      |                |         |               |         |
| Pf mono-infection                     | 102  | Reference       |         |               |         |
| Pv mono-infection                     | 280  | -0·08 (-0·29-0·12) | 0·43    |               |         |
| Pf & Pv coinfection                   | 14   | -0·06 (-0·56-0·44) | 0·81    |               |         |
| Pm mono-infection                     | 1    | -0·07 (-1·84-1·71) | 0·94    |               |         |
| Parasitaemia load                     |      |                |         |               |         |
| Lowest                                | 100  | Reference       |         |               |         |
| Lower middle                          | 87   | -0·12 (-0·38-0·14) | 0·37    |               |         |
| Higher middle                         | 103  | 0·05 (-0·19-0·30) | 0·67    |               |         |
| Highest                               | 107  | -0·09 (-0·33-0·16) | 0·47    |               |         |
| Treatment                             |      |                |         |               |         |
| DP                                    | 133  | Reference       |         | Reference      |         |
| ASMQ                                  | 129  | -0·015 (-0·23-0·20) | 0·89    | -0·04 (-0·24-0·16) | 0·72    |
| AL+                                   | 135  | 0·01 (-0·21-0·22)  | 0·96    | 0·06 (-0·14-0·25) | 0·56    |
| Total number of MiP                   | 397  | -0·17 (-0·25-0·10) | <0·0001 | -0·14 (-0·22-0·07) | 0·0001  |

* Adjusted for treatment groups.
## S17 Table. Birth outcomes in pregnant women who had malaria and were enrolled in the first trimester

| Baseline characteristic                  | DP             | ASMQ           | AL+             |
|-----------------------------------------|----------------|----------------|-----------------|
| Enrolled                                | 13             | 15             | 18              |
| Lost                                    | 1              | 1              | 3               |
| Miscarriage                             | 1/12           | 1/14           | 0/16            |
| Stillbirth                              | 0/11           | 1/13           | 0/15            |
| Congenital abnormality                  | 0/11           | 0/13           | 0/15            |
| EGA (week)                              | 39·9 (34·1-40·4) | 39·1 (34·3-40·4) | 39·5 (33·4-40·6) |
| Preterm birth                           | 1/11 (9%)      | 1/12 (8%)      | 3/15 (20%)      |
| Birth weight weighted in 3 days         | 8/11           | 9/12           | 13/15           |
| Birth weight (g)                        | 2730 (1739-3390) | 3170 (2500-3510) | 2920 (1580-3750) |
| Small-for-gestational age               | 2/7 (29%)      | 1/9 (11%)      | 4/12 (33%)      |
| Length (cm)                             | 48 (45-53) (n=8) | 50 (48-52) (n=9) | 49 (43-56) (n=12) |
| Placental weight (g)                    | 400 (190-580) (n=7) | 568 (460-680) (n=8) | 510 (250-912) (n=12) |

AL+: artemether-lumefantrine extended regimen, ASMQ: artesunate-mefloquine, DP: dihydroartemisinin-piperaquine, EGA: estimated gestational age.