Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sirima SB, Ogutu B, Lusingu JPA, et al. Comparison of artesunate–mefloquine and artemether–lumefantrine fixed-dose combinations for treatment of uncomplicated Plasmodium falciparum malaria in children younger than 5 years in sub-Saharan Africa: a randomised, multicentre, phase 4 trial. Lancet Infect Dis 2016; published online July 15. http://dx.doi.org/10.1016/S1473-3099(16)30020-2.
Appendix

Appendix Figure 1: Time-to-event analysis (Kaplan Meier) (mITT population) of ACPR rate

Survival Distribution Function

Time to failure (days)

0.00  0.25  0.50  0.75  1.00

STRATA: Treatment=AL  Treatment=ASMQ  Censored Treatment=AL  Censored Treatment=ASMQ

| Timepoint | Treatment | Number Failed | Number Left  | Survival | Failure | Test | Chi-Square | DF | P > Chi-Square |
|-----------|-----------|---------------|--------------|----------|---------|------|------------|----|--------------|
| At 20 days| ASMQ      | 4             | 434          | 0.5503   | 0.4497  |      |            |    |              |
|           | AL        | 3             | 450          | 0.5503   | 0.4497  |      |            |    |              |
| At 40 days| ASMQ      | 12            | 327          | 0.9860   | 0.0140  |      |            |    |              |
|           | AL        | 10            | 283          | 0.9728   | 0.0272  |      |            |    |              |
| At 60 days| ASMQ      | 17            | 237          | 0.9504   | 0.0496  | Log-Rank | 0.0646  | 1  | 0.6103       |
|           | AL        | 18            | 222          | 0.9410   | 0.0590  |      |            |    |              |
Appendix Table 1: Study Populations

| Population |
|------------|-----|-----|
| all randomised patients with informed consent & received either study medications at least once (ITT) | ASMQ | AL |
| | 472 | 472 |
| ITT modified by exclusion of patients with undetermined or missing PCR result (mITT) | | |
| | 446 | 444 |
| ITT subset of patients without a major protocol deviation, fully treatment-compliant & had a primary endpoint at day 63 or withdrew due to AE or lack of efficacy (PP) | | |
| | 407 | 407 |
| all randomised patients during first follow-up period and not receiving any rescue treatment, with informed consent, treated at least once with either study medication & having at least one clinical event relevant for safety assessment (SAF) | | |
| | 468 | 465 |
| all patients who switched from one study medication to the other after first parasitaemia recurrence & then undergoing 2nd follow-up (SAFrIP) | | |
| | 192 | 171 |
| all patients who switched to a rescue treatment that was not the alternative study medication after first parasitaemia recurrence & then undergoing 2nd follow-up (SAFrOth) | | |
| | 33 | 48 |

*a patient randomised to AL but receiving ASMQ was excluded from efficacy analyses but included in ASMQ safety population
### Appendix Table 2: Classification of malaria recurrences - at day 63 after PCR-based correction

|                      | ASMQ         | AL           |
|----------------------|--------------|--------------|
|                      | number of patients (%) |              |
| **ITT population**   |              |              |
| number of patients   | 472          | 472          |
| number of patients with recurrences | 214 (45·3) | 212 (44·9) |
| missing or undetermined\(a\) | 26 (12·1)   | 28 (13·2)   |
| recrudescence\(a\)  | 15 (7·0)     | 18 (8·5)     |
| re-infection\(a\)   | 173 (80·8)   | 166 (78·3)   |
| **PP population**    |              |              |
| number of patients   | 407          | 407          |
| number of patients with recurrences | 205 (50·4) | 205 (50·4) |
| undetermined\(a\)   | 21 (10·2)    | 23 (11·2)    |
| recrudescence\(a\)  | 15 (7·3)     | 17 (8·3)     |
| re-infection\(a\)   | 169 (82·4)   | 165 (80·5)   |

\(a\) percentage values indicate proportion of patients with infection recurrence.
### Appendix Table 3: Rate of vomiting within one hour<sup>a</sup> of drug intake (per day of treatment) (ITT population)

| treatment day | ASMQ | AL<sup>b</sup> | All | p-value<sup>c</sup> |
|---------------|------|----------------|-----|---------------------|
|               | number of patients vomiting / number of assessed patients (%) | | | |
| initial administration | | | | |
| day 0         | 43 / 460 (9·3) | 55 / 470 (11·7) | 98 / 930 (10·5) | 0·2424 |
| day 1         | 25 / 449 (5·6) | 21 / 462 (4·5)  | 46 / 911 (5·0)  | 0·4810 |
| day 2         | 14 / 442 (3·2) | 18 / 461 (3·9)  | 32 / 903 (3·5)  | 0·5492 |
| day 0 or day 1 or day 2 | 71 / 463 (15·3) | 79 / 471 (16·8) | 150 / 934 (16·1) | 0·5495 |
| re-administration<sup>d</sup> | | | | |
| day 0         | 4 / 43 (9·3) | 1 / 55 (1·8) | | |
| day 1         | 2 / 25 (8·0) | 2 / 21 (9·5) | | |
| day 2         | 1 / 14 (7·1) | 1 / 18 (5·6) | | |

<sup>a</sup>patients vomiting within 30 min or 30-60 min after intake; <sup>b</sup>rate includes patients vomiting after either of the 2 daily doses of AL; <sup>c</sup>derived from a Pearson Chi-squared test; <sup>d</sup>to patients who vomited after initial administration;
## Appendix Table 4: Classification of AEs for each of the three safety populations

|                                      | number of patients (%) | p-value<sup>a</sup> |
|--------------------------------------|------------------------|----------------------|
| **first 63-day follow-up, after start of treatment up to day 63 or until day before start of rescue treatment (SAFF)** |                        |                      |
| total                                | 468                    | 465                  | 933                |
| number with at least one AE          | 381 (81·4)             | 367 (78·9)           | 748 (80·2)         | 0·3667            |
| during treatment period              | 138 (29·5)             | 165 (35·5)           | 303 (32·5)         | 0·0590            |
| after treatment period               | 353 (75·4)             | 337 (72·5)           | 690 (74·0)         | 0·3322            |
| causing drug discontinuation         | 10 (2·1)               | 4 (0·9)              | 14 (1·5)           | 0·1763            |
| of moderate or greater intensity     | 252 (53·8)             | 222 (47·7)           | 474 (50·8)         | 0·0668            |
| possibly/probably/definitely-related to treatment | 46 (9·8) | 49 (10·5) | 95 (10·2) | 0·7462 |
| number with at least one SAE         | 8 (1·7)                | 10 (2·2)             | 18 (1·9)           | 0·6435            |
| during treatment period              | 5 (1·1)                | 2 (0·4)              | 7 (0·8)            | 0·4514            |
| after treatment period               | 3 (0·6)                | 8 (1·7)              | 11 (1·2)           | 0·1426            |
| leading to drug discontinuation      | 2 (0·4)                | 0 (0·0)              | 2 (0·2)            | 0·4995            |
| of moderate or greater intensity     | 11                     | 11                   | 22                 | -                 |
| possibly/probably/definitely-related to treatment | 1 | 0 | 0 | - |

| **second 63-day follow-up, after start of treatment with the alternative test treatment (SAFrIP)** |                        |                      |
| total                                | 192                    | 171                  | 363                |
| number with at least one AE          | 84 (43·8)              | 79 (46·2)            | 163 (44·9)         | 0·6731            |
| of moderate or greater intensity     | 41 (21·4)              | 43 (25·1)            | 84 (23·1)          | 0·4546            |
| number with at least one SAE         | 5 (2·6)                | 2 (1·2)              | 7 (1·9)            | 0·4541            |

| **second 63-day follow-up, after start of treatment with antimalarial other than ASMQ or AL (SAFrOth)** |                        |                      |
| total                                | 33                     | 48                   | 81                 |
| number with at least one AE          | 6 (18·2)               | 14 (29·8)            | 20 (24·7)          | 0·3038            |
| of moderate or greater intensity     | 6 (18·2)               | 10 (20·8)            | 16 (19·8)          | 1·0000            |
| number with at least one SAE         | 4 (12·1)               | 2 (4·2)              | 6 (7·4)            | 0·2186            |

AE, adverse event; SAE, serious adverse event; <sup>a</sup>Fisher’s exact test;