



Clinical trial results:

Phase 2/3, Open-Label, Comparative Trial Of Azithromycin Plus Chloroquine Versus Artemether-Lumefantrine For The Treatment Of Uncomplicated Plasmodium Falciparum Malaria In Children In Africa Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-004163-21 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 07 September 2010 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 27 April 2016 |
| First version publication date | 08 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A0661157 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00677833 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pfizer Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer Clinical Trials.gov Call Center, Pfizer Inc , 001 8007181021, ClinicalTrials.govCallCenter@pfizer.com |
| Scientific contact | Pfizer Clinical Trials.gov Call Center, Pfizer Inc , 001 8007181021, ClinicalTrials.govCallCenter@pfizer.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 August 2011 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 September 2010 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To confirm the hypothesis that azithromycin used in combination with chloroquine was non-inferior to artemether- Lumefantrine for the treatment of symptomatic, uncomplicated malaria due to Plasmodium Falciparum (P. Falciparum) in children in Africa.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 05 June 2008 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 2 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Ghana: 99 |
| Country: Number of subjects enrolled | Côte d'Ivoire: 30 |
| Country: Number of subjects enrolled | Mali: 80 |
| Country: Number of subjects enrolled | Burkina Faso: 90 |
| Country: Number of subjects enrolled | Kenya: 62 |
| Worldwide total number of subjects | 361 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 43 |

| | |
|---------------------------|-----|
| Children (2-11 years) | 309 |
| Adolescents (12-17 years) | 9 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited in 2 age-based Cohorts. Cohort 1= Subjects between 5-12 years of age, assumed to have some degree of immunity and at less risk for untoward outcome. After demonstration of successful treatment, safety and tolerability in Cohort 1, subjects between ≥ 6 months of age to ≤ 59 months of age were enrolled in Cohort 2.

Pre-assignment

Screening details:

Subjects were enrolled in 2 cohorts based on different age criteria. All Subjects in Cohort 1 met the age criteria whereas 3 Subjects enrolled in Cohort 2 were slightly older than 5 years (by less than 2 months).

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1: Azithromycin + Chloroquine |

Arm description:

Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. The combination tablets were administered on the basis of body weight approximately 30 milligram per kilogram (mg/kg) Azithromycin + approximately 10 mg base/kg Chloroquine base. Cohort 1 included subjects between greater than or equal to (\geq) 5 years of age and less than or equal to (\leq) 12 years of age.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Azithromycin/Chloroquine combination tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet (300 mg Azithromycin and 100 mg Chloroquine or 150 mg Azithromycin and 50 mg Chloroquine) on Days 0, 1, 2.

| | |
|------------------|-------------------------------------|
| Arm title | Cohort 1: Artemether + Lumefantrine |
|------------------|-------------------------------------|

Arm description:

Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. Cohort 1 included subjects between ≥ 5 years of age and ≤ 12 years of age.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Artemether/Lumefantrine combination tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet (20 mg Artemether and 120 mg Lumefantrine) on Days 0, 1, 2.

| | |
|------------------|--------------------------------------|
| Arm title | Cohort 2: Azithromycin + Chloroquine |
|------------------|--------------------------------------|

Arm description:

Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet on Days 0,

1, 2. The combination tablets were administered on the basis of body weight approximately 30 milligram/kilogram (mg/kg) Azithromycin + approximately 10 mg base/kg Chloroquine base. Cohort 2 included subjects between ≥ 6 months of age to ≤ 59 months of age.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Azithromycin/Chloroquine combination tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet (300 mg Azithromycin and 100 mg Chloroquine or 150 mg Azithromycin and 50 mg Chloroquine) on Days 0, 1, 2.

| | |
|------------------|-------------------------------------|
| Arm title | Cohort 2: Artemether + Lumefantrine |
|------------------|-------------------------------------|

Arm description:

Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. Cohort 2 included subjects between ≥ 6 months of age to ≤ 59 months of age.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Artemether/Lumefantrine combination tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet (20 mg Artemether and 120 mg Lumefantrine) on Days 0, 1, 2.

| Number of subjects in period 1 | Cohort 1: Azithromycin + Chloroquine | Cohort 1: Artemether + Lumefantrine | Cohort 2: Azithromycin + Chloroquine |
|---------------------------------------|--|---|--|
| Started | 55 | 51 | 124 |
| Completed | 51 | 51 | 122 |
| Not completed | 4 | 0 | 2 |
| Consent withdrawn by subject | 4 | - | 1 |
| Lost to follow-up | - | - | 1 |

| Number of subjects in period 1 | Cohort 2: Artemether + Lumefantrine |
|---------------------------------------|---|
| Started | 131 |
| Completed | 128 |
| Not completed | 3 |
| Consent withdrawn by subject | 3 |
| Lost to follow-up | - |

Baseline characteristics

Reporting groups

| | |
|--|--------------------------------------|
| Reporting group title | Cohort 1: Azithromycin + Chloroquine |
| Reporting group description: Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. The combination tablets were administered on the basis of body weight approximately 30 milligram per kilogram (mg/kg) Azithromycin + approximately 10 mg base/kg Chloroquine base. Cohort 1 included subjects between greater than or equal to (\geq) 5 years of age and less than or equal to (\leq) 12 years of age. | |
| Reporting group title | Cohort 1: Artemether + Lumefantrine |
| Reporting group description: Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. Cohort 1 included subjects between ≥ 5 years of age and ≤ 12 years of age. | |
| Reporting group title | Cohort 2: Azithromycin + Chloroquine |
| Reporting group description: Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. The combination tablets were administered on the basis of body weight approximately 30 milligram/kilogram (mg/kg) Azithromycin + approximately 10 mg base/kg Chloroquine base. Cohort 2 included subjects between ≥ 6 months of age to ≤ 59 months of age. | |
| Reporting group title | Cohort 2: Artemether + Lumefantrine |
| Reporting group description: Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. Cohort 2 included subjects between ≥ 6 months of age to ≤ 59 months of age. | |

| Reporting group values | Cohort 1: Azithromycin + Chloroquine | Cohort 1: Artemether + Lumefantrine | Cohort 2: Azithromycin + Chloroquine |
|---------------------------------------|--|---|--|
| Number of subjects | 55 | 51 | 124 |
| Age categorical Units: Subjects | | | |
| 6 months – less than 5 years | 0 | 0 | 123 |
| 5 years – 12 years | 55 | 51 | 1 |
| Gender categorical Units: Subjects | | | |
| Female | 28 | 21 | 50 |
| Male | 27 | 30 | 74 |

| Reporting group values | Cohort 2: Artemether + Lumefantrine | Total | |
|---------------------------------------|---|-------|--|
| Number of subjects | 131 | 361 | |
| Age categorical Units: Subjects | | | |
| 6 months – less than 5 years | 129 | 252 | |
| 5 years – 12 years | 2 | 109 | |
| Gender categorical Units: Subjects | | | |
| Female | 65 | 164 | |
| Male | 66 | 197 | |

End points

End points reporting groups

| | |
|--|--------------------------------------|
| Reporting group title | Cohort 1: Azithromycin + Chloroquine |
| Reporting group description: Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. The combination tablets were administered on the basis of body weight approximately 30 milligram per kilogram (mg/kg) Azithromycin + approximately 10 mg base/kg Chloroquine base. Cohort 1 included subjects between greater than or equal to (\geq) 5 years of age and less than or equal to (\leq) 12 years of age. | |
| Reporting group title | Cohort 1: Artemether + Lumefantrine |
| Reporting group description: Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. Cohort 1 included subjects between ≥ 5 years of age and ≤ 12 years of age. | |
| Reporting group title | Cohort 2: Azithromycin + Chloroquine |
| Reporting group description: Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. The combination tablets were administered on the basis of body weight approximately 30 milligram/kilogram (mg/kg) Azithromycin + approximately 10 mg base/kg Chloroquine base. Cohort 2 included subjects between ≥ 6 months of age to ≤ 59 months of age. | |
| Reporting group title | Cohort 2: Artemether + Lumefantrine |
| Reporting group description: Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. Cohort 2 included subjects between ≥ 6 months of age to ≤ 59 months of age. | |

Primary: Percentage of Subjects With Polymerase Chain Reaction (PCR)-Corrected Adequate Clinical and Parasitologic Response (ACPR) at Day 28 in the Modified Intent-to-treat (mITT) Population

| | |
|---|--|
| End point title | Percentage of Subjects With Polymerase Chain Reaction (PCR)-Corrected Adequate Clinical and Parasitologic Response (ACPR) at Day 28 in the Modified Intent-to-treat (mITT) Population ^[1] |
| End point description: ACPR(PCR-corrected) was defined as asexual <i>P. falciparum</i> parasitologic clearance at Day 28 irrespective of axillary, oral, rectal, or tympanic temperature, without previously meeting the criteria of Early Treatment Failure(ETF) or PCR-corrected Late Treatment Failure(LTF)(which includes PCR-corrected Late Clinical Failures[LCF]-see measure description in secondary outcome measure 9 and 10, and PCR-corrected Late Parasitologic Failures(LPF)- see measure description in secondary outcome measure 11 and 12).PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. mITT:treated subjects who met disease criteria(blood smears positive for <i>P.falciparum</i> mono-infection;asexual parasitemia=1000-100,000 parasites/microliter[mcL];fever/history of fever ≥ 38 degree Celsius[C][rectal],37.2 degree C[axillary] or ≥ 37.5 degree C[oral] within last 24 hours).Subjects in Ivory Coast center excluded from analysis. | |
| End point type | Primary |
| End point timeframe: Day 28 | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 126 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 89.27 (82.77 to 95.77) | 98.37 (95.59 to 100) | | |

Statistical analyses

| Statistical analysis title | ACPR (PCR-corrected) at Day 28 For mITT population |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

A two-sided 95 percent (%) confidence interval (CI) for the difference in ACPR (PCR corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR (PCR-corrected) proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. The drug (AZ-CQ) was considered non-inferior with respect to this primary endpoint if the lower bound of this 95% CI was $\geq -10\%$ points.

| | |
|---|--|
| Comparison groups | Cohort 2: Artemether + Lumefantrine v Cohort 2: Azithromycin + Chloroquine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -9.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.02 |
| upper limit | -2.18 |

Notes:

[2] - Null hypothesis: proportion of subjects with ACPR (PCR-corrected) of Azithromycin/Chloroquine (AZ-CQ) at Day 28 is less than that of Artemether/Lumefantrine (AL); Alternative hypothesis: proportion of subjects with ACPR (PCR-corrected) of AZ-CQ at Day 28 is greater than or equal (non-inferior) to that of AL by a non-inferiority margin of -0.1.

Primary: Percentage of Subjects With PCR-corrected ACPR at Day 28 in Per-Protocol (PP) Population

| | |
|-----------------|---|
| End point title | Percentage of Subjects With PCR-corrected ACPR at Day 28 in Per-Protocol (PP) Population ^[3] |
|-----------------|---|

End point description:

ACPR (PCR-corrected) was defined as asexual P.falciparum parasitologic clearance at Day 28 irrespective of axillary, oral, rectal, or tympanic temperature, without previously meeting the criteria of ETF (see measure description in secondary outcome measures 7 and 8) or PCR-corrected LTF (which includes PCR-corrected LCF - see measure description in secondary outcome measure 9 and 10, and PCR-corrected LPF - see measure description in secondary outcome measure 11 and 12). PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. Per-Protocol (PP) population was a subset of the mITT population, who received all 3 days of study medication to which they were assigned. For ACPR efficacy endpoints, subjects in Ivory Coast center excluded from PP population.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Day 28 | |

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 114 | 124 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 93.08 (87.32 to 98.84) | 99.16 (96.97 to 100) | | |

Statistical analyses

| Statistical analysis title | ACPR (PCR-corrected) at Day 28 For PP population |
|---|--|
| Statistical analysis description: A two-sided 95 percent (%) confidence interval (CI) for the difference in ACPR (PCR corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR (PCR-corrected) proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. The drug (AZ-CQ) was considered non-inferior with respect to this primary endpoint if the lower bound of this 95% CI was $\geq -10\%$ points. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -6.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.1 |
| upper limit | -0.05 |

Notes:

[4] - Null hypothesis: proportion of subjects with ACPR (PCR-corrected) of AZ-CQ at Day 28 is less than that of AL; Alternative hypothesis: proportion of Subjects with ACPR (PCR-corrected) of AZ-CQ at Day 28 is greater than or equal (non-inferior) to that of AL by a non-inferiority margin of -0.1.

Secondary: Percentage of Subjects With PCR-corrected ACPR in the mITT Population

| End point title | Percentage of Subjects With PCR-corrected ACPR in the mITT Population ^[5] |
|---|--|
| End point description: ACPR (PCR-corrected) was defined as asexual P.falciparum parasitologic clearance on Days 7, 14, 21, 35, 42 irrespective of axillary, oral, rectal, or tympanic temperature, without previously meeting the criteria of ETF (see measure description in secondary outcome measures 7 and 8) or PCR-corrected LTF (which includes PCR-Corrected LCF- see measure description in secondary outcome measure 9 and 10, and PCR-corrected LPF – see measure description in secondary outcome measure 11 and 12). PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. mITT population. For ACPR efficacy endpoints, subjects in Ivory Coast center excluded from mITT population. | |
| End point type | Secondary |

End point timeframe:

Days 7, 14, 21, 35, 42

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 126 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 7 | 94.17 (89.55 to 98.78) | 99.21 (97.25 to 100) | | |
| Day 14 | 92.47 (87.3 to 97.64) | 99.21 (97.24 to 100) | | |
| Day 21 | 91.59 (86.04 to 97.14) | 98.37 (95.65 to 100) | | |
| Day 35 | 89.27 (82.68 to 95.86) | 96.19 (91.85 to 100) | | |
| Day 42 | 87.55 (80.08 to 95.03) | 96.19 (91.79 to 100) | | |

Statistical analyses

| Statistical analysis title | Estimates for Day 7 |
|--|--|
| Statistical analysis description: A two-sided 95% CI for the difference in ACPR (PCR-corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. | |
| Comparison groups | Cohort 2: Artemether + Lumefantrine v Cohort 2: Azithromycin + Chloroquine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -5.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.93 |
| upper limit | -0.15 |

| Statistical analysis title | Estimates for Day 14 |
|----------------------------|----------------------|
|----------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-corrected) proportions [(AZ-CQ)-(AL)] using the

normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -6.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.15 |
| upper limit | -1.32 |

| | |
|---|--|
| Statistical analysis title | Estimates for Day 21 |
| Statistical analysis description: | |
| A two-sided 95% CI for the difference in ACPR (PCR-corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -6.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.82 |
| upper limit | -0.75 |

| | |
|---|--|
| Statistical analysis title | Estimates for Day 35 |
| Statistical analysis description: | |
| A two-sided 95% CI for the difference in ACPR (PCR-corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -6.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.59 |
| upper limit | 0.76 |

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Estimates for Day 42 |
|-----------------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -8.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.08 |
| upper limit | -0.18 |

Secondary: Percentage of Subjects With PCR-corrected ACPR in PP Population

| | |
|-----------------|--|
| End point title | Percentage of Subjects With PCR-corrected ACPR in PP Population ^[6] |
|-----------------|--|

End point description:

ACPR (PCR-corrected) was defined as asexual *P.falciparum* parasitologic clearance on Days 7, 14, 21, 35, 42 irrespective of axillary, oral, rectal, or tympanic temperature, without previously meeting the criteria of ETF (see measure description in secondary outcome measures 7 and 8) or PCR-corrected LTF (which includes PCR-corrected LCF - see measure description in secondary outcome measure 9 and 10, and PCR-corrected LPF - see measure description in secondary outcome measure 11 and 12). PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. PP population. For ACPR efficacy endpoints, subjects in Ivory Coast center were excluded from the PP population. Here "99999" in the CI signifies not available (NA). CI was not calculable as standard error for 100% rate could not be estimated from Kaplan-Meier method.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 7, 14, 21, 35, 42

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 114 | 124 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 7 | 98.25 (95.39 to 100) | 100 (-99999 to 99999) | | |
| Day 14 | 96.46 (92.59 to 100) | 100 (-99999 to 99999) | | |
| Day 21 | 95.53 (91.1 to 99.96) | 99.16 (97.03 to 100) | | |
| Day 35 | 93.08 (87.22 to 98.95) | 96.96 (92.9 to 100) | | |
| Day 42 | 91.29 (84.31 to 98.28) | 96.96 (92.84 to 100) | | |

Statistical analyses

| Statistical analysis title | Estimates for Day 21 |
|--|--|
| Statistical analysis description: A two-sided 95% CI for the difference in ACPR (PCR-corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -3.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.4 |
| upper limit | 1.14 |

| Statistical analysis title | Estimates for Day 35 |
|--|----------------------|
| Statistical analysis description: A two-sided 95% CI for the difference in ACPR (PCR-corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. | |

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -3.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.79 |
| upper limit | 3.04 |

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Estimates for Day 42 |
|-----------------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-corrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -5.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.55 |
| upper limit | 2.22 |

Secondary: Percentage of Subjects With PCR-uncorrected ACPR in the mITT Population

| | |
|-----------------|--|
| End point title | Percentage of Subjects With PCR-uncorrected ACPR in the mITT Population ^[7] |
|-----------------|--|

End point description:

ACPR (PCR-uncorrected) was defined as asexual *P.falciparum* parasitologic clearance on Days 7, 14, 21, 28, 35, 42 irrespective of axillary, oral, rectal, or tympanic temperature, without previously meeting the criteria of ETF (see measure description in secondary outcome measures 7 and 8) or PCR-uncorrected LTF (which includes PCR-uncorrected LCF - see measure description in secondary outcome measure 9 and 10, and PCR-uncorrected LPF - see measure description in secondary outcome measure 11 and 12). PCR-uncorrected: not adjusted for molecular testing which determined recrudescence or true failures from reinfection. mITT population. For ACPR efficacy endpoints, subjects in Ivory Coast center were excluded from mITT population.

| | |
|----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Days 7, 14, 21, 28, 35, 42 | |

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 126 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 7 | 94.17 (89.55 to 98.78) | 99.21 (97.25 to 100) | | |
| Day 14 | 89.08 (83.05 to 95.11) | 96.79 (93.28 to 100) | | |
| Day 21 | 67.87 (59.02 to 76.72) | 82.96 (75.91 to 90.01) | | |
| Day 28 | 51.55 (42.07 to 61.02) | 73.31 (65.1 to 81.52) | | |
| Day 35 | 44.67 (35.24 to 54.11) | 62.91 (54 to 71.82) | | |
| Day 42 | 37.8 (28.58 to 47.02) | 56.29 (47.12 to 65.46) | | |

Statistical analyses

| Statistical analysis title | Estimates for Day 7 |
|---|--|
| Statistical analysis description: | |
| A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -5.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.93 |
| upper limit | -0.15 |

| Statistical analysis title | Estimates for Day 14 |
|----------------------------|----------------------|
|----------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated

ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -7.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.54 |
| upper limit | -0.88 |

Statistical analysis title

Estimates for Day 21

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -15.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.24 |
| upper limit | -3.94 |

Statistical analysis title

Estimates for Day 28

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|-------------------|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
|-------------------|--|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -21.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -34.14 |
| upper limit | -9.39 |

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Estimates for Day 35 |
|-----------------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -18.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.05 |
| upper limit | -5.43 |

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Estimates for Day 42 |
|-----------------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 246 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -18.49 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.33 |
| upper limit | -5.65 |

Secondary: Percentage of Subjects With PCR-uncorrected ACPR in PP Population

| | |
|-----------------|--|
| End point title | Percentage of Subjects With PCR-uncorrected ACPR in PP Population ^[8] |
|-----------------|--|

End point description:

ACPR (PCR-uncorrected) was defined as asexual *P.falciparum* parasitologic clearance on Days 7, 14, 21, 28, 35, 42 irrespective of axillary, oral, rectal, or tympanic temperature, without previously meeting the criteria of ETF (see measure description in secondary outcome measures 7 and 8) or PCR-uncorrected LTF (which includes PCR-uncorrected LCF - see measure description in secondary outcome measure 9 and 10, and PCR-uncorrected LPF - see measure description in secondary outcome measure 11 and 12). PCR-uncorrected: not adjusted for molecular testing which determined recrudescence or true failures from reinfection. PP population. For ACPR efficacy endpoints, subjects in Ivory Coast center were excluded from the PP population. Here "99999" in the CI signifies not available (NA). CI is not calculable when rate is 100%.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 7, 14, 21, 28, 35, 42

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 114 | 124 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 7 | 98.25 (95.39 to 100) | 100 (-99999 to 99999) | | |
| Day 14 | 92.89 (87.69 to 98.08) | 97.56 (94.42 to 100) | | |
| Day 21 | 70.56 (61.67 to 79.45) | 83.62 (76.65 to 90.6) | | |
| Day 28 | 54.28 (44.57 to 63.98) | 73.9 (65.71 to 82.08) | | |
| Day 35 | 47.04 (37.31 to 56.77) | 63.41 (54.49 to 72.34) | | |
| Day 42 | 39.8 (30.24 to 49.36) | 56.74 (47.54 to 65.94) | | |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Estimates for Day 14 |
|----------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the

normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -4.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.6 |
| upper limit | 1.25 |

| | |
|---|--|
| Statistical analysis title | Estimates for Day 21 |
| Statistical analysis description: | |
| A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -13.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.21 |
| upper limit | -1.92 |

| | |
|---|--|
| Statistical analysis title | Estimates for Day 28 |
| Statistical analysis description: | |
| A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -19.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -32.16 |
| upper limit | -7.08 |

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Estimates for Day 35 |
|-----------------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -16.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.42 |
| upper limit | -3.33 |

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Estimates for Day 42 |
|-----------------------------------|----------------------|

Statistical analysis description:

A two-sided 95% CI for the difference in ACPR (PCR-uncorrected) proportions [(AZ-CQ)-(AL)] using the normal approximation to the binomial with continuity correction was constructed based on the estimated ACPR proportions from the Kaplan-Meier curves and their standard errors estimated by the greenwood formula.

| | |
|---|--|
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 238 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Kaplan-Meier curves |
| Parameter estimate | ACPR percent difference |
| Point estimate | -16.94 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.04 |
| upper limit | -3.83 |

Secondary: Percentage of Subjects With Early Treatment Failure (ETF) in the mITT Population (PCR-corrected)

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Early Treatment Failure (ETF) in the mITT Population (PCR-corrected) ^[9] |
|-----------------|---|

End point description:

ETF defined as subjects who met the following criteria:

1. Developed signs of severe malaria or clinical deterioration that required rescue medication on Days 0, 1, 2 or 3, in the presence of *P. falciparum* parasitemia
2. Last available asexual *P. falciparum* parasite count on Day 2 greater than the first available parasite count on Day 0 (Baseline), irrespective of axillary, oral or rectal temperature.
3. Parasitemia (*P. falciparum*) on Day 3 with fever or
4. Last available *P. falciparum* parasite count on Day 3 \geq 25% of the first available parasite count on Day 0 (Baseline).

PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. mITT population, subjects in Ivory Coast center were excluded from mITT population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 0 up to Day 3

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 126 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 5.83 | 0.79 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With ETF in PP Population (PCR-corrected)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With ETF in PP Population (PCR-corrected) ^[10] |
|-----------------|--|

End point description:

ETF defined as subjects who met the following criteria:

1. Developed signs of severe malaria or clinical deterioration that required rescue medication on Days 0, 1, 2 or 3, in the presence of *P. falciparum* parasitemia
2. Last available asexual *P. falciparum* parasite count on Day 2 greater than the first available parasite count on Day 0 (Baseline), irrespective of axillary, oral or rectal temperature.

3. Parasitemia (*P. falciparum*) on Day 3 with fever or
4. Last available *P. falciparum* parasite count on Day 3 $\geq 25\%$ of the first available parasite count on Day 0 (Baseline).

PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. PP population, subjects in Ivory Coast center were excluded from the PP population.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 0 up to Day 3 | |

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 114 | 124 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 1.75 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Late Clinical Failure (LCF) in the mITT Population (PCR-corrected)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Late Clinical Failure (LCF) in the mITT Population (PCR-corrected) ^[11] |
|-----------------|--|

End point description:

LCF included subjects who met any of the following criteria:

1. Development of signs of severe malaria or clinical deterioration requiring rescue medication after Day 3 in the presence of *P.falciparum* parasitemia, without previously meeting any of the criteria of ETF (see measure description in secondary outcome measures 5 and 6)

2. Presence of *P.falciparum* parasitemia and fever on any day from Day 4 onward, without previously meeting any of the criteria of ETF (see measure description in secondary outcome measures 5 and 6).

PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation.

mITT population, subjects in Ivory Coast center were excluded from mITT population.

| | |
|----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Days 7, 14, 21, 28, 35, 42 | |

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 126 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Day 7 | 0 | 0 | | |
| Day 14 | 0 | 0 | | |
| Day 21 | 0 | 0 | | |
| Day 28 | 0 | 0 | | |
| Day 35 | 0 | 0 | | |
| Day 42 | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With LCF in PP Population (PCR-corrected)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With LCF in PP Population (PCR-corrected) ^[12] |
|-----------------|--|

End point description:

LCF included subjects who met any of the following criteria:

1. Development of signs of severe malaria or clinical deterioration requiring rescue medication after Day 3 in the presence of *P.falciparum* parasitemia, without previously meeting any of the criteria of ETF (see measure description in secondary outcome measures 5 and 6)
 2. Presence of *P.falciparum* parasitemia and fever on any day from Day 4 onward, without previously meeting any of the criteria of ETF (see measure description in secondary outcome measures 5 and 6).
- PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation.

PP population, subjects in Ivory Coast center were excluded from the PP population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 7, 14, 21, 28, 35, 42

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 114 | 124 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Day 7 | 0 | 0 | | |
| Day 14 | 0 | 0 | | |
| Day 21 | 0 | 0 | | |
| Day 28 | 0 | 0 | | |
| Day 35 | 0 | 0 | | |

| | | | | |
|--------|---|---|--|--|
| Day 42 | 0 | 0 | | |
|--------|---|---|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Late Parasitologic Failure (LPF) in the mITT Population (PCR-corrected)

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Late Parasitologic Failure (LPF) in the mITT Population (PCR-corrected) ^[13] |
|-----------------|---|

End point description:

LPF: Presence of *P. falciparum* parasitemia in the mITT population on any day from Day 7 onward and the absence of fever without previously meeting any of the criteria of ETF (see measure description in secondary outcome measures 5 and 6) or LCF (see measure description in secondary outcome measure 7 and 8). PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. mITT population, subjects in Ivory Coast center were excluded from mITT population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 7, 14, 21, 28, 35, 42

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 126 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Day 7 | 0 | 0 | | |
| Day 14 | 1.67 | 0 | | |
| Day 21 | 2.5 | 0.79 | | |
| Day 28 | 4.17 | 0.79 | | |
| Day 35 | 4.17 | 2.38 | | |
| Day 42 | 5 | 2.38 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With LPF in PP Population (PCR-corrected)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With LPF in PP Population (PCR-corrected) ^[14] |
|-----------------|--|

End point description:

LPF: Presence of *P. falciparum* parasitemia in the PP population on any day from Day 7 onward and the absence of fever without previously meeting any of the criteria of ETF (see measure description in secondary outcome measures 5 and 6) or LCF (see measure description in secondary outcome measure 7 and 8). PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. PP population, subjects in Ivory Coast center were excluded from the PP population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 7, 14, 21, 28, 35, 42

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 114 | 124 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Day 7 | 0 | 0 | | |
| Day 14 | 1.75 | 0 | | |
| Day 21 | 2.63 | 0.81 | | |
| Day 28 | 4.39 | 0.81 | | |
| Day 35 | 4.39 | 2.42 | | |
| Day 42 | 5.26 | 2.42 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Asexual Parasitologic Response (PCR-corrected)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Asexual Parasitologic Response (PCR-corrected) ^[15] |
|-----------------|--|

End point description:

Percentage of Subjects who were cleared of asexual parasites. Asexual parasite clearance - clearance of asexual *P.falciparum* parasitemia within 7 days of initiation of treatment without subsequent recurrence (PCR-corrected) through the day of consideration. PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. mITT population. "n"=Subjects who were evaluable at specified time points for each arm, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 7, 14, 21, 28, 35, 42

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 ^[16] | 128 ^[17] | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Day 7 (n=120, 128) | 93.33 | 99.22 | | |
| Day 14 (n=120, 127) | 91.67 | 99.21 | | |
| Day 21 (n=120, 128) | 90.83 | 98.44 | | |
| Day 28 (n=120, 127) | 89.17 | 98.43 | | |
| Day 35 (n=120, 128) | 89.17 | 96.88 | | |
| Day 42 (n=120, 127) | 88.33 | 96.85 | | |

Notes:

[16] - Subjects with evaluable data, including subjects in Ivory Coast center.

[17] - Subjects with evaluable data, including subjects in Ivory Coast center.

Statistical analyses

| Statistical analysis title | Asexual Parasitologic Response for Day 7 |
|---|--|
| Statistical analysis description: Day 7. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -5.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.02 |
| upper limit | -0.75 |

| Statistical analysis title | Asexual Parasitologic Response for Day 14 |
|--|--|
| Statistical analysis description: Day 14. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -7.55 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.14 |
| upper limit | -1.95 |

| | |
|--|--|
| Statistical analysis title | Asexual Parasitologic Response for Day 21 |
| Statistical analysis description: Day 21. | |
| Comparison groups | Cohort 2: Artemether + Lumefantrine v Cohort 2: Azithromycin + Chloroquine |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -7.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.61 |
| upper limit | -1.6 |

| | |
|--|--|
| Statistical analysis title | Asexual Parasitologic Response for Day 28 |
| Statistical analysis description: Day 28. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -9.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.64 |
| upper limit | -2.87 |

| | |
|--|--|
| Statistical analysis title | Asexual Parasitologic Response for Day 35 |
| Statistical analysis description: Day 35. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |

| | |
|---|--|
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -7.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.45 |
| upper limit | -0.97 |

| | |
|--|--|
| Statistical analysis title | Asexual Parasitologic Response for Day 42 |
| Statistical analysis description: Day 42. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -8.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.43 |
| upper limit | -1.6 |

Secondary: Percentage of Subjects With Gametocytologic Response

| | |
|---|--|
| End point title | Percentage of Subjects With Gametocytologic Response ^[18] |
| End point description: Gametocyte response/absence/clearance: Clearance of P.falciparum gametocytemia (PCR-uncorrected) (attainment of 2 consecutive zero gametocyte counts) without subsequent recurrence through the day of consideration. PCR-uncorrected: not adjusted for molecular testing which determined recrudescence or true failures from reinfection. mITT population. "n"=subjects who were evaluable at specified time points for each arm, respectively. | |
| End point type | Secondary |
| End point timeframe: Days 7, 14, 21, 28, 35, 42 | |

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 ^[19] | 130 ^[20] | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Day 7 (n=122, 129) | 81.97 | 91.47 | | |
| Day 14 (n=122, 130) | 81.15 | 91.54 | | |
| Day 21 (n=122, 130) | 80.33 | 93.08 | | |
| Day 28 (n=122, 130) | 81.97 | 93.08 | | |
| Day 35 (n=122, 130) | 81.97 | 92.31 | | |
| Day 42 (n=122, 130) | 80.33 | 91.54 | | |

Notes:

[19] - Subjects with evaluable data, including subjects in the Ivory Coast center.

[20] - Subjects with evaluable data, including subjects in the Ivory Coast center.

Statistical analyses

| Statistical analysis title | Gametocytologic Response for Day 7 |
|---|--|
| Statistical analysis description: Day 7. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 252 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -9.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.27 |
| upper limit | -0.74 |

| Statistical analysis title | Gametocytologic Response for Day 14 |
|--|--|
| Statistical analysis description: Day 14. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 252 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -10.39 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.23 |
| upper limit | -1.55 |

| | |
|--|--|
| Statistical analysis title | Gametocytologic Response for Day 21 |
| Statistical analysis description: Day 21. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 252 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -12.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.45 |
| upper limit | -4.04 |

| | |
|--|--|
| Statistical analysis title | Gametocytologic Response for Day 28 |
| Statistical analysis description: Day 28. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 252 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -11.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.62 |
| upper limit | -2.6 |

| | |
|--|--|
| Statistical analysis title | Gametocytologic Response for Day 35 |
| Statistical analysis description: Day 35. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |

| | |
|---|--|
| Number of subjects included in analysis | 252 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -10.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.97 |
| upper limit | -1.71 |

| | |
|--|--|
| Statistical analysis title | Gametocytologic Response for Day 42 |
| Statistical analysis description: Day 42. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 252 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | large sample approximation to binomial |
| Parameter estimate | Percent difference |
| Point estimate | -11.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.14 |
| upper limit | -2.28 |

Secondary: Fever Clearance Time

| | |
|---|--------------------------------------|
| End point title | Fever Clearance Time ^[21] |
| End point description: Calculated as time of first occurrence of two consecutive time points with temperature less than (<) 38.0 degrees C/100.4 degrees Fahrenheit (F) (rectal), 37.2 degrees C/99.0 degrees F (axillary), or <37.5 degrees C/99.5 degrees F (oral). mITT population, including subjects in the Ivory Coast center. | |
| End point type | Secondary |
| End point timeframe: Baseline to Day 42 | |

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 131 | | |
| Units: Hours | | | | |
| median (full range (min-max)) | 24 (1 to 504) | 24 (1 to 336) | | |

Statistical analyses

| Statistical analysis title | Fever Clearance Time |
|--|--|
| Statistical analysis description: Time to event data was analyzed using the Kaplan-Meier curve. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2564 |
| Method | Kaplan-Meier, log rank |

Secondary: Asexual Plasmodium Falciparum Parasite Clearance Time

| End point title | Asexual Plasmodium Falciparum Parasite Clearance Time ^[22] |
|--|---|
| End point description: Defined as time to first of two consecutive zero asexual P. falciparum parasite (PCR-corrected) counts, regardless of recurrence of parasitemia later. PCR-corrected refers to the use of molecular testing to differentiate recrudescence from reinfection in the context of an efficacy evaluation. mITT population, including subjects in the Ivory Coast center. | |
| End point type | Secondary |
| End point timeframe: Baseline to Day 42 | |
| Notes: [22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments. | |

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 131 | | |
| Units: Hours | | | | |
| median (full range (min-max)) | 48 (24 to 504) | 24 (1 to 48) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Asexual P Falciparum Parasite Clearance Time |
| Statistical analysis description: Time to event data was analyzed using the Kaplan-Meier curve. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Kaplan-Meier, log rank |

Secondary: Nadir Hemoglobin Level

| | |
|--|--|
| End point title | Nadir Hemoglobin Level ^[23] |
| End point description: Nadir hemoglobin for each Subject was defined as the minimum hemoglobin values obtained from Day 0 through Day 3. mITT population, including Subjects in the Ivory Coast center. | |
| End point type | Secondary |
| End point timeframe: Day 0 through Day 3 | |

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 131 | | |
| Units: grams per deciliter (g/dL) | | | | |
| arithmetic mean (standard deviation) | 9.63 (± 1.53) | 9.82 (± 1.61) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Nadir Hemoglobin Level at Days 14, 28, and 42

| | |
|--|--|
| End point title | Change From Nadir Hemoglobin Level at Days 14, 28, and |
| End point description: Change from nadir= observation minus nadir. Nadir defined as the minimum value for each subject on Days 0-3. mITT population. "n"=subjects who were evaluable at specified time points for each arm, respectively. | |
| End point type | Secondary |
| End point timeframe: Day 14, 28, 42 | |

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 122 ^[25] | 128 ^[26] | | |
| Units: g/dL | | | | |
| arithmetic mean (standard error) | | | | |
| Change at Day 14 (n=122, 127) | 0.52 (± 0.11) | 0.44 (± 0.13) | | |
| Change at Day 28 (n=122, 127) | 1.15 (± 0.11) | 0.96 (± 0.13) | | |
| Change at Day 42 (n=122, 128) | 1.29 (± 0.12) | 1.14 (± 0.14) | | |

Notes:

[25] - Subjects with evaluable data, including subjects in the Ivory Coast center.

[26] - Subjects with evaluable data, including subjects in the Ivory Coast center.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Recurrence of Parasitemia

| | |
|-----------------|---|
| End point title | Time to Recurrence of Parasitemia ^[27] |
|-----------------|---|

End point description:

Time from the day of clearance to the time of recurrence of asexual *P.falciparum* parasitemia (PCR-uncorrected). mITT population, including subjects in the Ivory Coast center. Here "9.9999" indicates median as median time to recurrence could not be calculated for subjects in the Artemether-Lumefantrine treatment groups since fewer than 50% of the subjects experienced recurrent parasitemia during the study.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 0) to Day 42

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 131 | | |
| Units: Days | | | | |
| median (full range (min-max)) | 34 (2 to 42) | 9.9999 (7 to 43) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Time to Recurrence of Parasitemia |
| Statistical analysis description: Time to event data was analyzed using the Kaplan-Meier curve. | |
| Comparison groups | Cohort 2: Azithromycin + Chloroquine v Cohort 2: Artemether + Lumefantrine |
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 |
| Method | Kaplan-Meier, log rank |

Secondary: Number of Subjects With Recurrent Parasitemia Versus Baseline Plasmodium Falciparum Chloroquine Resistance Transporter (PfCRT) Status

| | |
|-----------------|---|
| End point title | Number of Subjects With Recurrent Parasitemia Versus Baseline Plasmodium Falciparum Chloroquine Resistance Transporter (PfCRT) Status ^[28] |
|-----------------|---|

End point description:

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: Baseline to Day 42 | |

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-----------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[29] | 0 ^[30] | | |
| Units: Subjects | | | | |

Notes:

[29] - Data for this outcome measure was not analyzed as per change in planned analysis.

[30] - Data for this outcome measure was not analyzed as per change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With PfCRT in True Failures

| | |
|-----------------|--|
| End point title | Percentage of Subjects With PfCRT in True Failures ^[31] |
|-----------------|--|

End point description:

A genetic marker, P.falciparum chloroquine resistance transporter (PfCRT), indicative of P.falciparum chloroquine resistance was to be determined from blood blots obtained on Day 0 and at the time of treatment failure. Treatment failure was defined as any of the following events that a subject experienced from Day 0 through the Day 42 visit: ETF (see measure description in secondary outcome measures 5 and 6), LCF (PCR corrected) (see measure description in secondary outcome measure 7 and 8), or LPF (PCR corrected) (see measure description in secondary outcome measure 9 and 10). Recrudescence of asexual P.falciparum parasites was considered treatment failure. Data for this outcome measure was not analyzed as per change in planned analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Day 42

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments.

| End point values | Cohort 2: Azithromycin + Chloroquine | Cohort 2: Artemether + Lumefantrine | | |
|-------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[32] | 0 ^[33] | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |

Notes:

[32] - Data for this outcome measure was not analyzed as per change in planned analysis.

[33] - Data for this outcome measure was not analyzed as per change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 35 days after last dose of study drug

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study. EU BR specific AE tables were generated separately using latest coding.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | COHORT1- AZITHROMYCIN/CHLOROQUINE |
|-----------------------|-----------------------------------|

Reporting group description:

Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. The combination tablets were administered on the basis of body weight approximately 30 milligram per kilogram (mg/kg) Azithromycin + approximately 10 mg base/kg Chloroquine base. Cohort 1 included subjects between ≥ 5 years of age and ≤ 12 years of age.

| | |
|-----------------------|----------------------------------|
| Reporting group title | COHORT1- ARTEMETHER/LUMEFANTRINE |
|-----------------------|----------------------------------|

Reporting group description:

Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. Cohort 1 included subjects between ≥ 5 years of age and ≤ 12 years of age.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | COHORT2- AZITHROMYCIN/CHLOROQUINE |
|-----------------------|-----------------------------------|

Reporting group description:

Azithromycin/Chloroquine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. The combination tablets were administered on the basis of body weight approximately 30 milligram/kilogram (mg/kg) Azithromycin + approximately 10 mg base/kg Chloroquine base. Cohort 2 included subjects between ≥ 6 months of age to ≤ 59 months of age.

| | |
|-----------------------|----------------------------------|
| Reporting group title | COHORT2- ARTEMETHER/LUMEFANTRINE |
|-----------------------|----------------------------------|

Reporting group description:

Artemether/Lumefantrine administered orally once daily for 3 days as a combination tablet on Days 0, 1, 2. Cohort 2 included subjects between ≥ 6 months of age to ≤ 59 months of age.

| Serious adverse events | COHORT1- AZITHROMYCIN/CHL OROQUINE | COHORT1- ARTEMETHER/LUMEF ANTRINE | COHORT2- AZITHROMYCIN/CHL OROQUINE |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 2 / 51 (3.92%) | 0 / 124 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------------------------|----------------------------------|-----------------------------------|
| Infections and infestations Hepatitis B subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 55 (0.00%) 0 / 0 0 / 0 | 1 / 51 (1.96%) 0 / 1 0 / 0 | 0 / 124 (0.00%) 0 / 0 0 / 0 |
| Malaria subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 55 (1.82%) 0 / 1 0 / 0 | 0 / 51 (0.00%) 0 / 0 0 / 0 | 0 / 124 (0.00%) 0 / 0 0 / 0 |
| Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 55 (0.00%) 0 / 0 0 / 0 | 1 / 51 (1.96%) 0 / 1 0 / 0 | 0 / 124 (0.00%) 0 / 0 0 / 0 |

| Serious adverse events | COHORT2- ARTEMETHER/LUME FANTRINE | | |
|--|---|--|--|
| Total subjects affected by serious adverse events subjects affected / exposed number of deaths (all causes) number of deaths resulting from adverse events | 1 / 131 (0.76%) 0 | | |
| Nervous system disorders Convulsion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 131 (0.76%) 0 / 1 0 / 0 | | |
| Infections and infestations Hepatitis B subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 131 (0.00%) 0 / 0 0 / 0 | | |
| Malaria subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 131 (0.00%) 0 / 0 0 / 0 | | |
| Sepsis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | COHORT1- AZITHROMYCIN/CHLOROQUINE | COHORT1- ARTEMETHER/LUMEFANTRINE | COHORT2- AZITHROMYCIN/CHLOROQUINE |
|---|--------------------------------------|-------------------------------------|--------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 55 (72.73%) | 36 / 51 (70.59%) | 103 / 124 (83.06%) |
| Vascular disorders | | | |
| Pallor | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Chills | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 2 / 51 (3.92%) | 3 / 124 (2.42%) |
| occurrences (all) | 2 | 2 | 3 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 2 / 51 (3.92%) | 0 / 124 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 3 / 124 (2.42%) |
| occurrences (all) | 0 | 1 | 3 |
| Product taste abnormal | | | |

| | | | |
|--|---------------------|----------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 1 / 124 (0.81%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 4 / 55 (7.27%) 4 | 3 / 51 (5.88%) 3 | 17 / 124 (13.71%) 20 |
| Reproductive system and breast disorders | | | |
| Balanoposthitis subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Vaginal inflammation subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 1 / 124 (0.81%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 4 | 6 / 51 (11.76%) 7 | 15 / 124 (12.10%) 16 |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 1 / 124 (0.81%) 1 |
| Epistaxis subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 4 | 0 / 51 (0.00%) 0 | 1 / 124 (0.81%) 1 |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 1 / 51 (1.96%) 1 | 4 / 124 (3.23%) 4 |
| Tachypnoea subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 1 / 124 (0.81%) 1 |
| Psychiatric disorders | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| Irritability subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Restlessness subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Investigations Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 1 / 51 (1.96%) 1 | 0 / 124 (0.00%) 0 |
| Injury, poisoning and procedural complications Scratch subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 1 / 51 (1.96%) 1 | 0 / 124 (0.00%) 0 |
| Thermal burn subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Wound subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 2 / 51 (3.92%) 3 | 2 / 124 (1.61%) 2 |
| Congenital, familial and genetic disorders Phimosis subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 1 / 51 (1.96%) 1 | 1 / 124 (0.81%) 1 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Headache | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 8 / 55 (14.55%) 9 | 5 / 51 (9.80%) 7 | 4 / 124 (3.23%) 4 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 2 / 124 (1.61%) |
| occurrences (all) | 0 | 1 | 2 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 1 | 1 |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 3 / 51 (5.88%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 3 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 2 / 51 (3.92%) | 0 / 124 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Eye disorders | | | |
| Conjunctival pallor | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye swelling | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 55 (18.18%) | 5 / 51 (9.80%) | 4 / 124 (3.23%) |
| occurrences (all) | 11 | 5 | 6 |
| Abdominal pain upper | | | |

| | | | |
|--|------------------|----------------|-------------------|
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Anal pruritus | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Colitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 1 / 51 (1.96%) | 4 / 124 (3.23%) |
| occurrences (all) | 2 | 2 | 4 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal sounds abnormal | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Mucous stools | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 2 / 51 (3.92%) | 0 / 124 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 11 / 55 (20.00%) | 5 / 51 (9.80%) | 38 / 124 (30.65%) |
| occurrences (all) | 12 | 6 | 44 |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis atopic | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-----------------|----------------|-----------------|
| Pruritus | | | |
| subjects affected / exposed | 9 / 55 (16.36%) | 1 / 51 (1.96%) | 8 / 124 (6.45%) |
| occurrences (all) | 9 | 1 | 8 |
| Pruritus generalised | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 2 / 124 (1.61%) |
| occurrences (all) | 0 | 0 | 2 |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 2 / 124 (1.61%) |
| occurrences (all) | 0 | 0 | 2 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Swelling face | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 51 (1.96%) | 1 / 124 (0.81%) |
| occurrences (all) | 1 | 1 | 1 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Pain in extremity | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Amoebiasis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Blister infected | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body tinea | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 51 (0.00%) | 4 / 124 (3.23%) |
| occurrences (all) | 1 | 0 | 4 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 3 / 51 (5.88%) | 3 / 124 (2.42%) |
| occurrences (all) | 0 | 3 | 3 |
| Dysentery | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 1 | 1 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|-----------------------------|------------------|------------------|-------------------|
| Furuncle | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 2 / 124 (1.61%) |
| occurrences (all) | 0 | 0 | 2 |
| Giardiasis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Helminthic infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatitis A | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infection parasitic | | | |
| subjects affected / exposed | 14 / 55 (25.45%) | 11 / 51 (21.57%) | 37 / 124 (29.84%) |
| occurrences (all) | 14 | 11 | 39 |
| Malaria | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 4 / 51 (7.84%) | 26 / 124 (20.97%) |
| occurrences (all) | 5 | 4 | 26 |
| Mumps | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 0 / 51 (0.00%) | 0 / 124 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 1 / 124 (0.81%) |
| occurrences (all) | 0 | 0 | 1 |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 51 (1.96%) | 0 / 124 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 51 (0.00%) | 2 / 124 (1.61%) |
| occurrences (all) | 0 | 0 | 2 |

| | | | |
|---|----------------------|---------------------|-----------------------|
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 2 / 124 (1.61%) 3 |
| Rhinitis subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | 1 / 51 (1.96%) 1 | 2 / 124 (1.61%) 2 |
| Septic rash subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Skin infection subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 1 / 51 (1.96%) 1 | 0 / 124 (0.00%) 0 |
| Staphylococcal skin infection subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Subcutaneous abscess subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Tinea capitis subjects affected / exposed occurrences (all) | 5 / 55 (9.09%) 5 | 2 / 51 (3.92%) 2 | 2 / 124 (1.61%) 2 |
| Tonsillitis subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 1 / 51 (1.96%) 1 | 0 / 124 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 55 (10.91%) 6 | 4 / 51 (7.84%) 4 | 9 / 124 (7.26%) 13 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 0 / 51 (0.00%) 0 | 0 / 124 (0.00%) 0 |
| Viral rash subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 51 (0.00%) 0 | 1 / 124 (0.81%) 1 |
| Metabolism and nutrition disorders Decreased appetite | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 55 (5.45%) | 3 / 51 (5.88%) | 9 / 124 (7.26%) |
| occurrences (all) | 3 | 3 | 10 |

| | | | |
|---|---|--|--|
| Non-serious adverse events | COHORT2- ARTEMETHER/LUME FANTRINE | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 99 / 131 (75.57%) | | |
| Vascular disorders | | | |
| Pallor | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 3 / 131 (2.29%) | | |
| occurrences (all) | 3 | | |
| Chills | | | |
| subjects affected / exposed | 5 / 131 (3.82%) | | |
| occurrences (all) | 5 | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 131 (2.29%) | | |
| occurrences (all) | 3 | | |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Malaise | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Product taste abnormal | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 27 / 131 (20.61%) | | |
| occurrences (all) | 31 | | |
| Reproductive system and breast | | | |

| | | | |
|---|------------------|--|--|
| disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vaginal inflammation | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 13 / 131 (9.92%) | | |
| occurrences (all) | 14 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Irritability | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Restlessness | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|--|--|--|
| Investigations Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) | 0 / 131 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Scratch subjects affected / exposed occurrences (all) Thermal burn subjects affected / exposed occurrences (all) Wound subjects affected / exposed occurrences (all) | 0 / 131 (0.00%) 0 1 / 131 (0.76%) 1 1 / 131 (0.76%) 1 | | |
| Congenital, familial and genetic disorders Phimosis subjects affected / exposed occurrences (all) | 0 / 131 (0.00%) 0 | | |
| Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all) | 0 / 131 (0.00%) 0 1 / 131 (0.76%) 2 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 0 / 131 (0.00%) 0 4 / 131 (3.05%) 4 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphadenopathy | 4 / 131 (3.05%) 4 | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Conjunctival pallor | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye swelling | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Periorbital oedema | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 14 / 131 (10.69%) | | |
| occurrences (all) | 16 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anal pruritus | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Colitis | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 131 (6.11%) | | |
| occurrences (all) | 8 | | |
| Enteritis | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Gastrointestinal sounds abnormal | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mucous stools | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 13 / 131 (9.92%) | | |
| occurrences (all) | 14 | | |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|-----------------|--|--|
| Rash | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Swelling face | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Amoebiasis | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Blister infected | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Body tinea | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Bronchitis | | | |
| subjects affected / exposed | 9 / 131 (6.87%) | | |
| occurrences (all) | 9 | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Dysentery | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Fungal skin infection | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Furuncle | | | |
| subjects affected / exposed | 5 / 131 (3.82%) | | |
| occurrences (all) | 6 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 5 / 131 (3.82%) | | |
| occurrences (all) | 6 | | |
| Giardiasis | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Helminthic infection | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Hepatitis A | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Infection parasitic | | | |
| subjects affected / exposed | 31 / 131 (23.66%) | | |
| occurrences (all) | 33 | | |
| Malaria | | | |
| subjects affected / exposed | 19 / 131 (14.50%) | | |
| occurrences (all) | 19 | | |
| Mumps | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Otitis media acute | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 8 / 131 (6.11%) | | |
| occurrences (all) | 8 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Septic rash | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Tinea capitis | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | | |
| occurrences (all) | 2 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 12 / 131 (9.16%) | | |
| occurrences (all) | 14 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | | |
| occurrences (all) | 1 | | |
| Viral rash | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 131 (3.82%) | | |
| occurrences (all) | 5 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 18 December 2007 | <ol style="list-style-type: none">1. The primary endpoint was changed from asexual <i>P. falciparum</i> parasite clearance rate at Day 28 to adequate clinical and parasitological response (ACPR) at Day 282. The primary endpoint (ACPR) was also changed to be based on PCR-corrected data rather than using uncorrected data.3. Secondary endpoint changed from % Late treatment failure (LTF) to % Late Clinical Failures (LCF) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| Cohort 1 was a screening cohort, meant for safety evaluation, but not included in the efficacy assessments. |
|---|

Notes: